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Archives of Internal Medicine

VOLUME 50 JULY, 1932 NUMBER 1

DIFFUSE HEMORRHAGE FROM THE STOMACH

EDWARD L. BORTZ, M.D.
PHILADELPHIA

Diffuse bleeding from the gastric mucosa is regarded as a relatively unimportant phenomenon and is rarely, if ever, considered in the bedside diagnosis of patients afflicted with hematemesis. When the patient vomits blood, the differential diagnosis, as a rule, takes into consideration the following possibilities:

The Most Common Causes of Gastric Hemorrhage

A. *Neoplasms:*
- Carcinoma
- Polypi

B. *Ulcers:*
- Acute
- Subacute and progressive
- Chronic

C. *Infections—Acute or Chronic* (May cause either a local ulcer or a diffuse gastritis):
1. Intra-abdominal (colitis, enteritis, gastritis)
   - appendicitis
   - disease of the biliary tract
   - tuberculosis
   - typhoid
2. Extra-abdominal
   - scarlet fever
   - yellow fever
   - measles
   - cellulitis
   - pneumonia
   - diphtheria
   - endocarditis
3. Disease of the upper respiratory tract
4. Pelvic disease
5. Alcoholism

D. *Systemic Diseases:*
1. Cardiovascular
   - heart failure
   - endocarditis
   - thromboses or emboli
   - hypertension
   - aneurysms
   - ruptured varices
     - esophagus
     - rectum and anus (especially)

From the Medical Service of the Lankenau Hospital.

2. Blood dyscrasias
   leukemia
   the purpuras
3. Renal disease
4. Cirrhosis
5. Syphilis
6. Allergy (urticaria)

E. *Corrosion:*

From ingestion of poisons, as chloride, iodine, lye, etc.

The clinical syndrome which characterizes each of the aforementioned states is so definite that little difficulty should be experienced in narrowing the diagnosis to the logical underlying lesion. However, the certitude of successful diagnosis is more apparent than real. The survey of a large number of cases in which the outstanding sign was hematemesis suggests that hemorrhage from the stomach may arise from one or more of several different mucosal lesions and may be due to other inciting factors.

1. DIFFUSE GASTRIC HEMORRHAGE DUE TO PHYSICAL OR EMOTIONAL STRAIN

Warren [1] in 1881 noted that the female sex seems to suffer from hematemesis more frequently than the male, that it may occur at any age, and that sometimes it seems to take place spontaneously but really is due to some exciting cause that in itself might be insufficient to produce hemorrhage in a sound gastric membrane but is able to effect a rupture when any tendency to hemorrhage already exists. Under this heading he mentioned mental excitement, strain, concussions of the body and overdistentions of the stomach. He believed that injurious pressure could come on the internal organs, causing various forms of trouble, especially in women, and cited the following case:

> A woman, 25 years of age, taught in the public schools and lived at home with her parents. She had no hereditary predisposition to any disease and always considered herself healthy in every respect. After taking singing lessons by the "Abdominal Method or Elocution Breathing" for a while, she was troubled by what she thought was dyspepsia, and she took the usual remedies, without benefit. Five months after the onset of this gastric distress and the day after taking a lesson, she vomited over a pint of dark, bloody fluid. Within the next ten days there were seven recurrences of hematemesis, the blood being at times bright red and at times dark. This patient was given medical treatment in her home, and the hemorrhage finally ceased.

Alvarez [2] cited a case in which diffuse gastric hemorrhage occurred from an apparently healthy mucous membrane due to mental excitement.

1. Warren, E. L.: Gastrorrhagia and Hematemesis, with a Case, Boston M. & S. J. **104**:417, 1881.

2. Alvarez, W. C.: Nervous Indigestion, New York, Paul B. Hoeber, Inc., 1931, p. 58.

A man, an inventor, after years of poverty induced one of the richest industries of the country to accept his machine. The patient saw wealth and comfort within his grasp, but a few months later, with a change in the raw product that was being refined, the machine clogged and the company ordered that it be taken out. The patient immediately had a severe gastric hemorrhage. The defect in the machine was overcome; again it failed, and again it was remodeled. This happened at least six times in three years, and on each occasion the patient had a severe hemorrhage.

In both the foregoing cases, the hemorrhage ceased spontaneously, the interior of the stomach was not examined, and the condition present

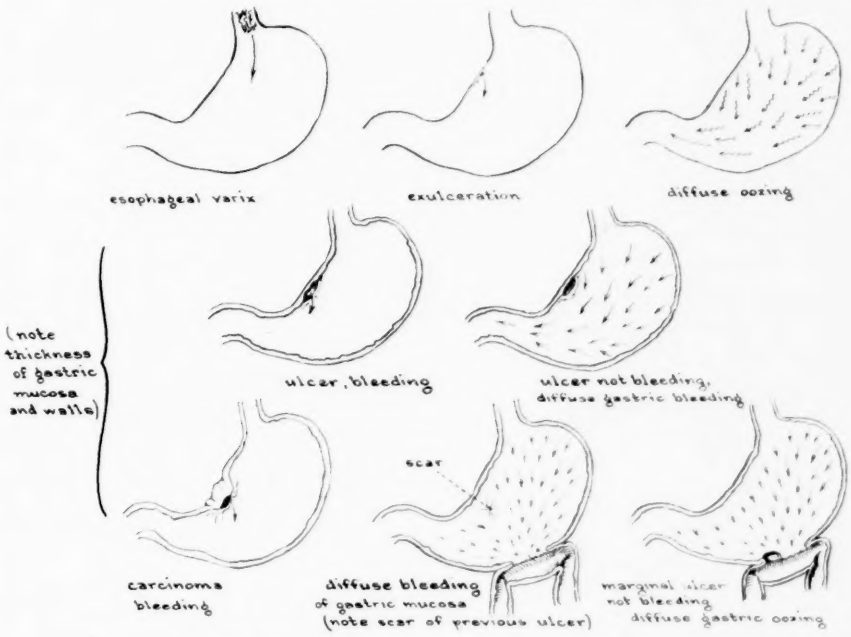
esophageal varix
exulceration
diffuse oozing
(note thickness of gastric mucosa and walls)
ulcer, bleeding
ulcer not bleeding, diffuse gastric bleeding
scar
carcinoma bleeding
diffuse bleeding of gastric mucosa (note scar of previous ulcer)
marginal ulcer not bleeding diffuse gastric oozing

Fig. 1.—Types of gastric hemorrhage. Gastric hemorrhage may arise from a local lesion, such as a ruptured varix, an ulcer or a neoplasm; diffuse oozing or frank hemorrhage can take place. A chronic ulcer, a marginal ulcer or an ulcer scar has been noted in the mucosa, the seat of diffuse bleeding with no hemorrhage from the ulcer itself.

in the mucosa is not known. In the following case reported by Mayo Robson,[3] which may possibly be of the same kind, the inner surface of the stomach was actually examined and the type of bleeding noted.

3. Robson, A. W. M., and Moynihan, B. G. A.: Diseases of the Stomach and Their Surgical Treatment, ed. 2, New York, William Wood & Company, 1904, p. 278.

A married woman, aged 28, while in her home suddenly felt faint and vomited a pint of dark, clotted blood. She seemed to improve under medical treatment, but six days later vomited another large quantity of blood and had melena. Four days after the second attack (the tenth day of the illness) the hematemesis recurred. Since it was evident that the hemorrhage was persisting, the stomach was opened and many bleeding points were found in the mucosa. Three were ligatured *en masse*, and a posterior gastro-enterostomy was performed. The patient was able to be out of bed in the third week and to leave the house within the month. She rapidly regained her strength, had no further hemorrhage and remained in good health.

This patient had been operated on a few months previously for varicose veins, and six weeks previously had had an attack of influenza. However, she felt quite well, and the day before the first hematemesis had been out hunting. It seems probable that in this case it was the strain of hunting that caused the rupture of the capillary walls.

2. PROFUSE HEMORRHAGE FROM SUPERFICIAL DEFECTS IN THE MUCOSA

Dieulafoy [4] in 1897 wrote the classic description of the lesion since known as "Dieulafoy's ulcer," a lesion so shallow that at operation as well as post mortem it might pass unperceived without careful examination and a preconceived idea that it was to be found. Only the mucosa was involved (in some cases, including the muscularis mucosae), the edges were neither raised nor thick, and the surrounding tissue was healthy. Often, near the lesion or at its surface, small spots of ecchymotic appearance were noted which were described as miliary abscesses situated in the depths of the mucosa and forcing their way into the cavity of the stomach. At times, the arteriole that was the source of the hemorrhage could be distinguished.

Dieulafoy's first experience with the condition was as follows:

A man, 27 years of age, had had a severe hematemesis, accompanied by pain in the stomach, brought on by lifting a heavy load of papers. After ruling out all the other common causes of severe gastric hemorrhage, it was decided that the hematemesis in this case was due to a gastric ulcer that had evolved without symptoms. The hematemesis reappeared during the night, and it was estimated that the patient had lost about 4 liters of blood in less than twenty-four hours. At 1 o'clock the next afternoon, he died in the midst of another violent hemorrhage. At autopsy, it was only after washing the mucosa with care that a very superficial "exulceration" about the size of a silver dollar was discovered 2 cm. from the cardia. The surface of the lesion was a whitish gray with two or three small ecchymotic spots and two crateriform erosions, one of which revealed a small gaping arteriole in which the point of a pin might be introduced and which could be plainly seen only through the microscope. The remainder of the gastric mucosa was in perfect integrity, as was that of the duodenum and esophagus. The

4. Dieulafoy, G.: Exulceratio simplex, Clin. méd. de Hôtel-Dieu de Paris, 1897-1898, vol. 2, lectures 1, 2 and 3.

arteriole was a branch of the gastric coronary artery and had been perfectly healthy when it was attacked by the ulcerous process. The adjacent veins were dilated and thrombosed and explained the ecchymotic spots.

Dieulafoy's second case was as follows:

A man, 22 years of age, was taken with malaise and nausea as he was "returning peacefully home after dining well" and soon afterward vomited "floods of blood." The next day, in order to regain his strength he ate a great deal of food,

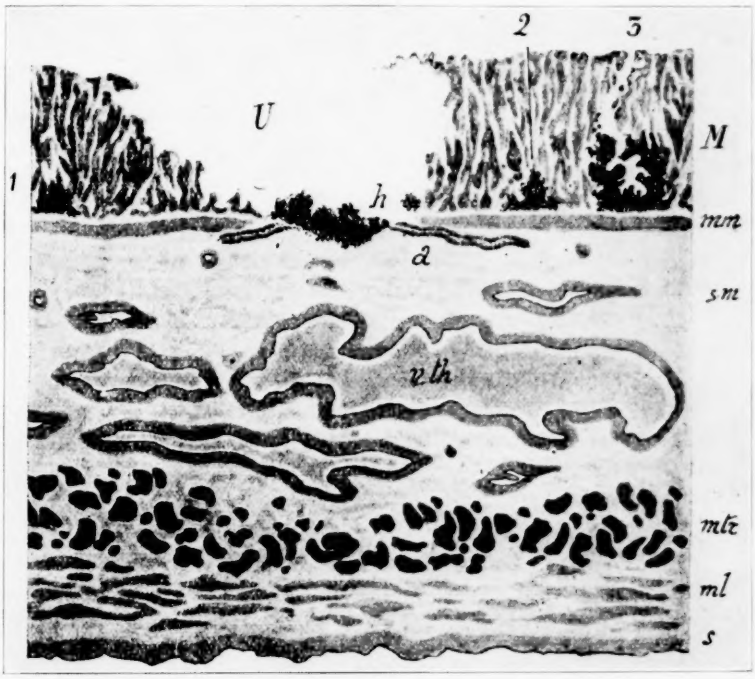

Fig. 2.—Illustration from Dieulafoy's original paper (Clinique médicale de l'Hôtel-Dieu de Paris, Paris, Masson & Cie, 1898, vol. 2), showing the details of the ulcerative process. Note the hemorrhage (*h*) and the thrombosed veins (*v. th.*). *U* indicates ulceration at the expense of the mucosa (*M*) and of the muscularis mucosa (*mm*); *a*, a submucous arteriole destroyed at point *h*, where are to be found many new corpuscles in heaps; at this point have occurred the fatal hemorrhages; *s.m.*, the submucous layer, *mtr* and *ml*, muscular layers; *s*, serosa and *1*, *2* and *3*, miliary abscesses lying in the depth of the mucosa.

especially meat. At 2 o'clock the following morning there was a recurrence of the hematemesis, after which for several days he had no gastric symptoms, pain or vomiting, but was extremely feeble and finally went to the hospital. The patient had never had any symptoms of ulcer; there was nothing to suggest precirrhosis or cirrhosis, heart disease, tuberculosis, etc., so Dieulafoy made a diagnosis of

"exulceration." After two days another severe hematemesis occurred, and since medical treatment had failed in the first case, it was decided to operate. When the stomach was opened, it was only after sponging the mucosa with the greatest care that a shallow exulceration, only as big as a dime, was seen. When lightly rubbed with a tampon, hemorrhage immediately appeared from a surface 2 inches (5 cm.) in diameter. The bleeding section was infolded and sutured; the patient gradually recovered and several months later was in perfect health.

Dieulafoy appears to have considered these cases as identical, but Mayo Robson pointed out that they represent two different kinds of lesions. In the first case described, the lesion was more extensive and the surface layers were removed to such an extent that the arterioles running under the muscularis mucosae were exposed. In the second case there was a mere abrasion of the surface epithelium, which, though so small as to be scarcely perceptible to the naked eye, gave rise to the most severe hemorrhages. Mayo Robson stated that such abrasions may be overlooked post mortem, but, as seen when hemorrhage is going on, the mucous membrane seems to be studded with numerous bleeding points. However, in Dieulafoy's case it must be recognized that there was profuse bleeding from a fairly large area and that the epithelial abrasion was probably secondary to the hemorrhage.

3. HEMORRHAGE FROM A PORELIKE OPENING INTO ONE OF THE GASTRIC VESSELS

Smith[5] in 1902 described an unusual lesion which he claimed to have found in a number of cases. This was a small erosion, no larger than a pinhead, which did not spread superficially but led directly into an open vessel and could be detected only on the closest scrutiny. He reported a case as follows:

A woman, 22 years of age, was admitted to the hospital with a condition diagnosed as bleeding gastric ulcer, after having had two severe hematemeses. At operation, no ulcer was found, but in the mucosa there was a "villous looking patch" about the size of a quarter from which blood was oozing. The bleeding section was tied off by a purse-string suture; the patient at first did well, but later developed suppurative parotitis with edema of the glottis necessitating tracheotomy. She started vomiting blood again and died soon afterward. At postmortem examination it was noted that the old affected region was effectually sequestrated, but near the pylorus was a small porelike opening into one of the gastric vessels with no trace to the naked eye of any ulceration, swelling or pathologic condition other than a simple solution of continuity in the mucous membrane.

4. HEMORRHAGE FROM MULTIPLE MINUTE EROSIONS

The condition known as "Einhorn's disease[6]" is characterized by multiple erosions of the inner surface of the stomach, which, however,

5. Smith, F. J.: Gastric Ulcer, M. Press & Circ. **14**:539, 1902.

6. Einhorn, M.: Diseases of the Stomach, ed. 7, New York, William Wood & Company, 1929, p. 294.

bleed very little. If gastric lavage is performed when the patient is in a fasting state, one or more small pieces of mucous membrane are observed of a blood red color and about 0.3 or 0.4 cm. long and nearly as wide. Under the microscope, these fragments show well preserved glands and accumulations of red blood corpuscles. Only rarely is any blood noted, and this is usually when coughing spells occur during the lavage. The fragments partly or wholly peel off from the mucosa some time previous to the washing, which explains why there is no bleeding during the lavage. It is a question whether the exfoliations always take place at the same spots, the tissue constantly becoming replaced and peeling off, or whether most of the surface is affected to such an extent that small pieces of mucosa peel off here and there. Whether from the same spot or not, these exfoliations take place day by day in the stomach and effect temporary erosions. The chief symptoms are pain and a feeling of weakness. The pain is never intense; it occurs immediately after meals, is independent of the character of the food, persists for one or two hours and disappears gradually. Usually intervals of variable duration occur during which the patient is perfectly well. These patients are always treated medically, and the interior of the stomach has never been examined.

Aschoff [7] described a type of erosions, the so-called stigmas of Beneke, which are localized predominantly in the region of the greater curvature and may be so thickly scattered that countless small erosions are found. They are usually the size of a pinhead or slightly larger, only exceptionally reaching a greater diameter, and are of a peculiar wedge shape with a central loss of substance. They are found in all age periods and seem to have a definite relationship to nervous diseases. Beneke [8] expressed the belief that nervous arterial spasm causes small anemic necroses of the mucous membrane, followed by an injurious action of the gastric juice with digestion of the capillaries and hemorrhage. In some instances, the anatomic observations may be completely negative and the condition designated as "parenchymatous gastric hemorrhage." The ischemia is a transitory phenomenon and may be followed by hyperemia or normal circulation. Some authors have described a spastic contraction of the muscularis mucosae as the cause of the arterial blocking and the anemic necrosis; others find the cause more in constitutional, nutritional and circulatory disturbances. A summary of a case of this type reported by Jonas [9] follows:

7. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

8. Beneke, R.: Ueber die hämorrhagischen Erosionen des Magens (Stigmata ventriculi), Verhandl. d. deutsch. path. Gesellsch. **12**:284, 1908.

9. Jonas, A. F.: Operation for Ulcus Ventriculi Chronicum: Three Cases, with Remarks on Indications for Operation, West. M. Rev. **2**:285, 1897.

A German, 32 years of age, a butcher, married, had four sisters and six brothers. His father had died of stomach trouble of fifteen years' duration, and the oldest brother complained of gastric disturbances; the other brothers and sisters were well. The patient's illness had begun fifteen years previously with "cramps" in the stomach, lasting but a short time, and recurring at irregular intervals, most frequently in the summer. About three and a half years before admission to the hospital he began vomiting small amounts of blood, which from time to time increased in amount. All heavy foods, such as potatoes, bread and meat, caused "cramps," and he was obliged to discontinue the use of beer and wine because of the pain produced, which was usually relieved by emesis. During the last year emesis was not so frequent, but was much larger in quantity and consisted mostly of blood. Constipation was severe, requiring enormous doses of cathartics for relief. For more than two years he had been unable to work; for five months he had been almost constantly in bed; during the last four years he could lie only on his left side, and his weight had dropped from 200 to 130 pounds (90.7 to 59 Kg.).

On physical examination, the abdomen appeared rather full, with the greatest prominence about the umbilicus and a marked depression at the epigastrium. Peristaltic waves were very marked. Slight tapping on the left side of the umbilicus excited gastric peristalsis, which increased rapidly and produced pain sufficient to cause the patient to resume a sitting posture. The contents of the stomach were removed by a tube; there were almost 2 liters; the substance was a dark brown, with a coffee ground sediment, and contained undigested curdled milk and coagulated white of egg, which had been taken the night before. The empty stomach was filled with atmospheric air so that its outline might be distinctly traced, and seemed to fill nearly one-third of the abdominal cavity, its greater curvature filling the left hypochondrium and extending downward nearly a hand-breadth below and to the right of the umbilicus. The pylorus could be felt as an indurated mass. The abdomen was opened, and an incision parallel with the long axis of the pylorus showed that the lumen was pervious for an ordinary lead pencil; the pyloric wall was five-eighths inch (0.9 cm.) in thickness. The remainder of the stomach was not examined.

On the night of the fourth day after operation, the patient became restless and died suddenly. At autopsy, the stomach was enormously distended and contained nearly a gallon of bloody fluid with a large quantity of coffee ground material. After repeated examination, "a very large number of very small ulcers" were found in the hepatic end of the stomach together with innumerable small cicatrices, the former seat of ulcers. The pylorus was occupied by a dozen or more larger scars, and its wall was thickened with a mass of newly-formed connective tissue, but there were no recent ulcerations. All the other organs seemed normal. The immediate cause of death was given as renewed hemorrhage from the innumerable ulcerations.

The early history, the pyloric stenosis and the exaggerated gastric peristalsis would suggest a nervous origin in this case; the family history suggests a constitutional factor of some sort. Also, one wonders if in Einhorn's disease the interior of the stomach with its multiple tiny exfoliations might present an appearance similar to that described by Aschoff.

5. CAPILLARY OOZING

During the early years of the twentieth century, a number of eminent English physicians and surgeons [10] called attention to another type of condition, occurring in young women, in which although bleeding from the gastric mucous membrane had lasted for years, the most minute examination of the interior of the stomach might fail to show any lesion. It was stated that the essence of the disease was a liability to gastric hemorrhage independent of ulceration. The attacks of bleeding varied much in severity, being sometimes comparatively trifling but often severe, and at times extending over a period of many years with intervals of months or even a year or two between the attacks. These patients very often were or had been chlorotic and showed the symptoms variously known as "anemic dyspepsia," "chlorotic dyspepsia," etc. Hale White remarked that severe dyspeptic symptoms are commoner with chlorosis than with other anemias, and consist of hematemesis, persistent vomiting aside from the hematemesis and pain in the region of the stomach. These cases were often diagnosed as peptic ulcer, but the patients were not liable to the numerous serious complications of gastric ulcer. They might have been in perfect health at the time of the first hemorrhage and continued to look healthy, since there were fairly long intervals between the attacks. The prognosis was good, although relapses were frequent; the hematemesis was rarely fatal, and the attacks gradually ceased after 40 years of age.

In the following typical cases the interior of the stomach was actually examined:

A woman, 27 years of age, had a history of indigestion and pain after taking food for eight years. She had been in another hospital the year before for these symptoms. For the past two months the pain had been continuous and she had had occasional hematemesis to a small amount. On the day of admission, she vomited a pint of blood; on the following day, there was another hematemesis, and four days later another. She improved under medical treatment for one month, then had a recurrence of the symptoms followed in a fortnight by a return of the hematemesis. A month later, there was another attack of hematemesis. The

10. White, W. H.: Are Not Some Patients Said to be Afflicted with Gastric Ulcer Really Suffering from a Different Disease? Lancet **1**:1819, 1901. Herringham, W. P.: A Lecture on Haematemesis, Clin. J. **27**:337, 1906. Dawson, Bertrand: The Diagnosis of Gastric Ulcer, Brit. M. J. **2**:1032, 1905. Armstrong, G. E.: The Wisdom of Surgical Interference in Haematemesis and Melena from Gastric and Duodenal Ulcer, ibid. **2**:1087, 1899. Hood, D. W. C.: Haematemesis, with Special Reference to That Form Met With in Early Adult Female Life, Tr. M. Soc. London **15**:283, 1892. Mansell Moullin, C. W.: Three Cases of Gastrotomy for Haematemesis, Lancet **2**:1125, 1900; The After History of Patients upon Whom Gastric Operations Have Been Performed, Brit. M. J. **1**:1037, 1905. Robson, A. W. M.: Discussion of the Surgical Treatment of Haematemesis, Lancet **2**:1626, 1902.

improvement seemed so slight that it was believed wise to operate. The stomach was turned practically inside out, but nothing was found to be the matter with it.

A woman, aged 33, was seized without premonitory symptoms with violent hematemesis; the hemorrhage recurred four days later and again three days following the second attack. The patient had been married three months, had been anemic and had had slight indigestion, but otherwise did not consider herself ill. Since the bleeding resisted the ordinary remedies, surgical intervention was advised. An incision was made in the axis of the stomach, and seven bleeding points were found in the mucosa. Two that were bleeding freely were taken up by artery forceps and the mucous membrane ligatured *en masse;* the others stopped on exposure to the air. A posterior gastro-enterostomy was performed. At the end of the second week, the patient was able to take solid food, and a year later had had no recurrence and was well in every respect.

A woman, 23 years of age, had pain, vomiting, hematemesis, a tender epigastrium and anemia, but no wasting. The first attack occurred in August, 1900, when she was in bed for two months; the second attack was in February, 1901, and lasted six weeks; the third attack occurred in January, 1902, and the fourth in July, 1904, at which time she was operated on. All that was found was a small oozing erosion on the posterior wall of the stomach, which was ligated. After the operation, there were many fresh hemorrhages and the patient's condition was not improved. A second operation was performed for another attack of hematemesis, but the attacks had continued until the case was reported.

Hale White stressed that in these cases the origin of the hemorrhage was not a local lesion, but that the blood oozed from multiple points in a mucosa that usually presented an unbroken surface. When minute erosions or ecchymoses were noted, he believed they were the result rather than the cause of the hemorrhage and were due to the blood tearing through the epithelial lining.

6. "HEMORRHAGIC GASTRALGIA"

Closely associated with the chlorotic type, there were cases reported of older women with chronic symptoms, in whom the interior of the stomach showed "slight catarrhal inflammation," "congestion" or some other condition which seemed altogether inadequate to account for the serious nature of the bleeding. White proposed the name "hemorrhagic gastralgia" as being suitable for some of these.

The following case was originally reported by Thompson:[11]

A woman, aged 38, gave a classic history of gastric pain, epigastric tenderness, distress after eating and repeated attacks of hematemesis, with increasing weakness and emaciation, the symptoms lasting through many months. The patient had several serious attacks of hematemesis after admission to the hospital, and at the end of two weeks, since there was no improvement in her condition, the stomach was opened and the interior thoroughly explored with an electric

11. Thompson, W. G.: Hematemesis from Gastric Ulcer: Notes on Over Two Hundred Cases, Am. J. M. Sc. **130**:375, 1905.

light. The mucosa appeared slightly granular and congested, but there was no cicatrix and no sign of any ulcer. The incision was therefore closed and the patient died three days later from exhaustion following repeated vomiting.

The first case we have to report is of this type:

A woman, aged 38, was admitted to the Lankenau Hospital in May, 1922, with a history of indigestion and vomiting for eleven years, becoming progressively worse during the last three or four years and lasting from three to four days with intervals of one month between the attacks. She experienced severe pain and belching of gas immediately after eating; occasionally vomiting or alkalis would bring relief. Menstruation was regular, and she was never jaundiced. She complained of headache all the time, which was worse during the attacks. Two weeks before admission, she had diarrhea and melena with occasional expectoration of blood. On physical examination, tenderness was noted in both the epigastric and the appendical regions. Her teeth were in good condition; the lungs were clear throughout. The temperature on admission was 99.6 F. and varied while she was in the hospital between 98 and 99.4 F., with a pulse rate of from 80 to 104.

The patient was operated on by Dr. John B. Deaver, and a chronically diseased appendix was removed. The stomach was incised; the mucosa was congested, granular and oozed blood, but no trace of ulcer could be found. She was given duodenal feedings for about five weeks, followed by a soft diet and milk by mouth.

The relevant laboratory findings in this case were as follows: The blood count showed 70 per cent hemoglobin, 4,000,000 erythrocytes and 18,700 leukocytes, with 83 per cent polymorphonuclears, 15 per cent lymphocytes and 2 per cent large mononuclears. The urine was normal. The phenolsulphonphthalein test gave 72 per cent elimination, with 45 per cent the first hour, 19 per cent the second and 8 per cent the third. The blood sugar was 89 mg. per hundred cubic centimeters of blood. The Wassermann reaction was negative. An x-ray picture of the gastro-intestinal tract showed no definite evidence of demonstrable pathologic change. Gastric analysis by the fractional test meal was within normal limits.

Since being discharged, the patient has communicated regularly with the follow-up department of the hospital. The gastric pain persisted after the operation, though not so severe as before, and there were occasional attacks of vomiting but no hematemesis until October, 1924. In May, 1925, she experienced regurgitations of blood; in May, 1926, she vomited a large amount of "black material," and in December of that year she had an attack of vomiting of dark brown and black fluid. The follow-up report for June 15, 1927, stated that the patient was quite well until March 1, when she started vomiting blood; she had been in bed off and on since then and had severe pains just after eating, but her general appearance was good. From that time, although the gastric symptoms persisted, there was no hematemesis until November, 1929, when she vomited blood for two weeks with constant pain in her stomach made worse by the taking of food or fluid. An x-ray picture of the stomach and duodenum made at this time was negative.

The patient has continued in this state up to the time of writing this article. Although the bleeding is not constant, it is persistent, and it may be assumed that during the attacks the condition in the gastric mucosa found nine years ago at operation is still present.

In the literature there are reported numerous similar cases occurring in male subjects, two of which follow:[12]

A man, 36 years of age, had suffered for several years from cardialgia and nausea. On July 5, he had a sudden profuse hematemesis; a diagnosis of gastric ulcer was made, and he was given treatment for ulcer for two months. However, gastric pain was constant throughout the summer, with frequent vomiting. On September 16 and 18, after test breakfasts, the laboratory reports showed a large amount of mucus, free hydrochloric acid and no organic acids. On September 22, the patient complained of severe pain in the stomach and vomited from 800 to 1,000 cc. of nearly fresh blood. The stomach was opened, and systematic exploration revealed a superficial erosion 1 cm. in size and three smaller erosions. All these points were ligated; the patient recovered and left the hospital on November 3. He had no further hemorrhages, but continued to suffer from gastralgia and a dilated stomach, which resisted all treatment.

A man, 28 years of age, had been in the hospital three times in three years for treatment of gastric ulcer. During the last admission, he had medical treatment for one month, but hematemesis, melena and hiccups persisted. At operation, exploration of the stomach and as much of the duodenum as possible was negative. A gastro-enterostomy with suture was performed. Vomiting continued after the operation, and the patient died on the fifth day. Postmortem examination showed a slight lesion of the mucosa 1 cm. square, situated 4 cm. from the pylorus, and general peritonitis.

7. DIFFUSE BLEEDING AS A RECURRENCE AFTER OPERATION FOR ULCER

Diffuse bleeding may occur from the gastric wall from one to ten years after operation. Fitzgerald[13] reported the following case:

A man, a clerk, 34 years of age, who had been operated on for a perforated ulcer on the anterior wall of the duodenum, made a good recovery and was discharged "well." Almost seven years later, he was readmitted because of blood in the stool and a feeling of profound weakness; a second operation revealed half a dozen areas of hemorrhage in the mucosa of the stomach, but no ulceration, acute or old, could be found. Part of the stomach and the first part of the duodenum were removed; the patient recovered, and two years later was in excellent general health, with no indigestion and no hemorrhages.

The second case I wish to report seems to be of this type:

A man, 38 years of age, who was employed as a bank runner for a bond house, was admitted to the Lankenau Hospital four days after having had a sudden severe

12. Andrews, E. W., and Eisendrath, D. N.: On the Surgical Treatment of Hemorrhage from Gastric Ulcers, Ann. Surg. **30**:393, 1899. Lund, F. B.; Joslin, E. P., and Murphy, F. T.: Operations upon Benign Diseases of the Stomach at the Boston City Hospital and Massachusetts General Hospital 1898-1903, inc., Boston M. & S. J. **91**:113, 1904.

13. Fitzgerald, R. R.: Chronic Follicular Gastritis: With a Report of Nine Cases, Brit. J. Surg. **19**:25, 1931.

hematemesis while sitting at dinner, without apparent cause and with no associated pain. He fainted and was carried to a sofa, and soon afterward the hematemesis recurred. He regained consciousness and except for exhaustion felt all right. He was advised to come to the hospital at once, but for three days went to his work as usual; during this time, the stools were black, but there was no gross bleeding from the rectum. On the fourth day, he fainted again and reported at the clinic.

He had had measles, whooping cough and scarlet fever with no complications in childhood and an appendectomy in 1916, but claimed to have been in good health until 1918, when he was gassed and wounded slightly in the elbow while in France. A few months later, while still in the army, he had bronchopneumonia; tuberculosis developed and he was in the hospital most of the year 1919. He then began to have pain in his stomach, which was fairly continuous and griping and was worse after meals; he vomited his food, but there was no blood either in the vomitus or in the stools. Most of 1920 was spent in a sanatorium; the pain in the stomach persisted, and jaundice with clay-colored stools developed. In 1921, hemorrhoidectomy and gastro-enterostomy for ulcer (?) were performed, after which the condition of the lung healed, the pain disappeared from his stomach and he had no vomiting; he seemed to be in good condition until January, 1926, when Dr. Deaver removed his gallbladder after one week of severe griping pain. Gallstones were present. A few months later he started vomiting again, usually about one hour after meals, with nausea but no pain; the vomitus consisted of mucus, bile and undigested food. From 1926 until February, 1931, when he was admitted to the hospital, he had had about nine such spells each year; he was ill for only a few hours, then recovered and felt quite well.

Physical examination revealed a tender area in the epigastrium, with increased resistance, and palpation in that region made him weak and nauseated. In the left lower quadrant a mass was palpable, which was soft, movable, smooth and tender and was said to feel like a spastic sigmoid. The heart was normal except for a very faint systolic murmur. Percussion revealed the lungs resonant throughout, slight impairment at the left apex posteriorly, no râles, normal breath sounds and decreased rhonchal fremitus posteriorly at the left apex, with a suggestion of whispered pectoriloquy.

The blood count, on many tests, showed erythrocytes, from 2,680,000 to 1,360,000, with from 50 to 30 per cent hemoglobin, and from 4,800 to 11,000 leukocytes; from 62 to 74 per cent neutrophils, from 16 to 31 per cent lymphocytes, from 5 to 8 per cent large mononuclears, from 1 to 2 per cent transitionals and 1 per cent eosinophils. The Wassermann and Kahn reactions were negative; the Gruskin test for carcinoma gave negative results. The urine was normal; all examinations of the feces were positive for blood, showing from a faint to a very heavy trace. An x-ray picture of the chest for foci of infection was interpreted as showing an old peribronchial infiltrate extending from both hili generally throughout both lungs. Both upper lobes, particularly both first interspace trunks, were cottony on their periphery, suggesting old localized lesions, but not sufficiently definite for a diagnosis of present activity.

From the history, it was thought that this patient had a marginal ulcer. He had previously been operated on for ulcer, and he had two classic attacks simulating perforation while he was in the hospital. He was given four transfusions of blood, but in spite of all therapeutic measures, he went into shock and died on the twelfth day after admission.

At autopsy, the lungs were negative for active tuberculous lesions, and in the stomach there was no ulcer or perforation as was expected, but in the mucosa

proximal to the perfect gastro-enterostomy were a large area of tiny petechial hemorrhages and a smaller similar area near the gastro-enterostomy. There was no evidence of ulcer in the gastro-intestinal canal and no scar in the duodenum. It seems doubtful that the patient ever had an ulcer.

Several types of gastric bleeding have been described, all of them probably etiologically distinct from those listed in the foregoing tabulation, namely:

1. Diffuse gastric hemorrhage due to physical or emotional strain
2. Profuse hemorrhage from superficial defects in the mucosa

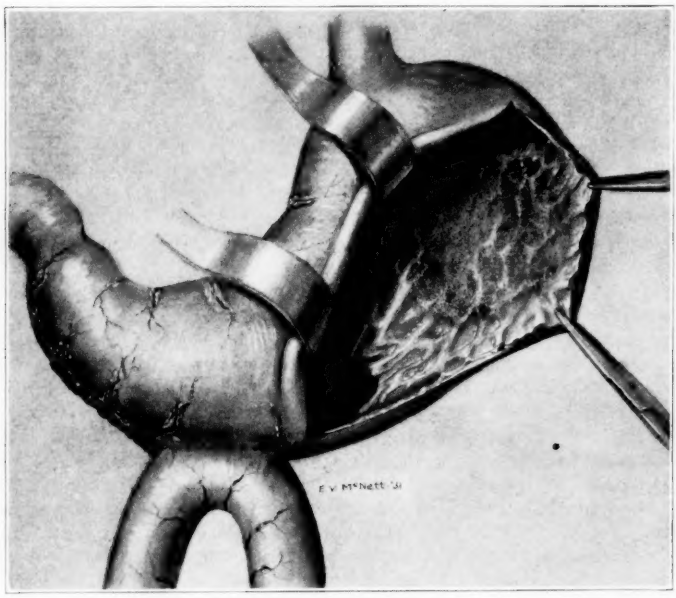

Fig. 3.—The numerous minute bleeding points from which hemorrhage sufficient to cause a fatal issue took place.

3. Hemorrhage from a porelike opening into one of the gastric vessels
4. Hemorrhage from multiple minute erosions
5. Capillary oozing
6. "Hemorrhagic gastralgia"
7. Diffuse bleeding as a recurrence after operation for ulcer

In the accompanying table are listed thirty-six additional cases, in each of which the stomach was opened and the mucosa carefully examined.

Observations in Thirty-Six Additional Cases

Age	Sex*	Comment	Result	Reported by
..	♀	Hematemesis for 1 month to the extent of 30 ounces; mucosa showed several losses of substance so shallow and velvety they were not strikingly different from rest of stomach	Death	Abbe (New York M. J. **53**: 519, 1891)
35	♀	Copious hematemesis for 7 days; good previous health; no symptoms of ulcer; mucosa showed oozing from 3 points, resembling linear fissures in 2 cases and stellate fissure in third; around fissures over area of 1 cm. was an apparent loss of epithelium	Complete recovery	Armstrong [10]
31	♀	Indigestion and pain 2 years with repeated vomiting of small quantities of blood; no ulcer found in stomach; all symptoms except hematemesis recurred after operation	Recovery	Rodman (Philadelphia M. J. **5**: 1302, 1900)
27	♀	Epigastric pain and vomiting 8 years about 1 hour after eating; hematemesis at 3 and 4 year intervals, and monthly for 5 months before admission; several small points oozing blood and at cardiac end an area 2 inches square on the anterior wall	Good recovery	Rodman (Philadelphia M. J. **5**: 1302, 1900)
36	♀	Sausage poisoning 2 years previously; repeated gastric hemorrhage; vomited all solid food; circular constriction about pylorus and stomach dilated; no ulceration	Recovery	Rodman (Philadelphia M. J. **5**: 1302, 1900)
29	♀	Epigastric pain for 3 years ½ hour after eating; 18 months previously vomited coffee ground material; 2 days previously hematemesis, 4 ounces, and constant hematemesis from that time; physical examination negative except for localized tenderness in epigastrium; mucosa showed several areas oozing blood	Death	Lund, Joslin and Murphy [12]
23	♀	Previous history unimportant; 36 hours before admission vomited blood and showed melena, repeated 3 times; 2 small bleeding areas near incision probably due to trauma, but no evidence of ulceration	Death	Lund, Joslin and Murphy [12]
21	♀	Every symptom of gastric ulcer with repeated hematemesis and characteristic pain; interior of stomach showed slight catarrhal inflammation	Death	Hale White (Lancet **2**: 1189, 1906)
21	♀	Sudden severe hematemesis with recurrences; developed parotitis and died of hyperpyrexia; no source of bleeding in esophagus, stomach or bowel	Death	Hood [13]
25	♀	Pain, vomiting, hematemesis; stomach opened, no visible pathologic changes	Complete recovery	Hood [13]
34	♀	Severe hematemesis and melena; no history of dyspepsia or vomiting after food; abdomen not tender; one very small area oozing blood on posterior wall near pylorus	Recovery	Mansell Moullin [14]
37	♀	Gastric pain, vomiting and hematemesis for 7 years; died in midst of hemorrhage; careful search failed to show any source for bleeding; stomach sent to museum	Death	Hale White (Lancet **2**: 1189, 1906)
..	♀	Pain, vomiting and hematemesis for years; no source of bleeding or ulcer in stomach	Excellent recovery	Hale White (Lancet **2**: 1189, 1906)
41	♂	Pain in epigastrium not related to food, vomiting, copious hematemesis, melena; well 2 years and had recurrence with more persistent hematemesis; 4 pinpoint hemorrhages near pylorus	Death	Hale White (Lancet **2**: 1189, 1906)
30	♀	Periodic pain and vomiting after food for 12 years; 3 years previously had profuse hematemesis; small abrasion from which blood was oozing; no return of hematemesis after operation, but pain and vomiting continued	Recovery	Dawson [15]

* In this column, ♂ indicates male; ♀, female

Observations in Thirty-Six Additional Cases—Continued

Age	Sex*	Comment	Result	Reported by
28	♀	Skin tenderness and deep tenderness in epigastrium; pain, vomiting, hematemesis; recurrent symptoms for 11 years; congested patch of mucosa	Recovery	Dawson [10]
28	♀	History of acute gastric pain, hematemesis, melena; stomach appeared normal; cause of death could not be determined	Death	Thompson [11]
31	♀	Good previous health; "indigestion" for 14 days; hematemesis day previously, and severe hematemesis on day of admission; at operation, stomach turned more or less inside out; mucosa deep red all over and seemed to bleed wherever it was touched; patient died of shock; at autopsy, slight erosion seen at cardiac end in middle of which was a small opened vein with a thrombus formed in its lumen	Death	Herringham [10]
36	♀	In hospital 8 years previously for gastric pain and vomiting; well 2 years; hematemesis; bleeding points in stomach found and ligated; 8 weeks after operation severe hematemesis and another later	Recovery	Herringham [10]
54	♀	For many years had abdominal pain, vomiting and dyspepsia; hematemesis after admission and 10 days later severe and fatal hematemesis; no ulcer, erosion or bleeding point found in stomach or intestine, the mucous membrane of which appeared quite healthy	Death	Hale White (Lancet **2**: 1189, 1906)
44	♀	Indigestion 25 years; sudden hematemesis and melena, repeated soon after; did not feel ill but had some epigastric pain; 3 small bleeding points at commencement of duodenum cauterized and arteries of greater curvature ligated; at autopsy, stomach and duodenum appeared absolutely normal	Death	Hale White (Lancet **2**: 1189, 1906)
18	♂	Strong, healthy with unimportant previous history; suddenly vomited 2½ pints of blood and melena; 5 days later vomited 1½ pints; 5 days after that 1 pint; patch on posterior wall oozing blood from a few minute points and slightest touch produced further hemorrhage anywhere in area; mucosa otherwise normal	Death	Hale White (Lancet **2**: 1189, 1906)
19	♀	Pain after eating for several weeks; vomited large quantity of blood; 4 recurrences in 12 hours; operation showed no ulcer	Recovery	Hale White (Lancet **2**: 1189, 1906)
47	♀	Stomach and duodenum explored for ulcer but none found; posterior gastrojejunostomy satisfactory, but condition not improved; still had hematemesis and melena, but these disappeared if kept in bed and put on milk diet	Recovery	Hale White (Lancet **2**: 1189, 1906)
33	♀	Pain and vomiting for 4 years with hematemesis once; no ulcer or scar in stomach; gastrojejunostomy; symptoms returned 5 months later and persisted; postoperative hematemesis once	Recovery	Mansell Moullin [10]
24	♀	Pain, vomiting and hematemesis for 4 years; looked quite healthy; mucosa carefully examined, but appeared perfectly healthy; blood count 5,400,000, with normal hemoglobin	Recovery	Mansell Moullin [10]
32	♀	For several years had pain in stomach; many attacks of hematemesis during 9 months; looked quite healthy; interior of stomach and duodenum thoroughly explored; no abnormality seen	Complete recovery	Hale White (Lancet **2**: 1189, 1906)
23	♀	Cramps in stomach for some time; sudden copious hematemesis and melena; small erosion traversed by open arteriole	Death	Dieulafoy [4]
20	♀	Excellent previous health and good constitution; sudden violent hematemesis and melena; very superficial erosion in mucosa with open arteriole	Death	Dieulafoy [4]

* In this column, ♂ indicates male; ♀, female.

Observations in Thirty-Six Additional Cases—Continued

Age	Sex*	Comment	Result	Reported by
30	♀	Sudden hematemesis; superficial loss of substance in mucosa	Death	Dieulafoy [4]
35	♂	Gastric pain for several months; expectorated few streaks of blood and short time later died without even vomiting; 2 liters of blood in stomach and ecchymotic spot found near cardia	Death	Dieulafoy [4]
..	♀	Three or four stellate ecchymoses from 1 to 2.5 cm. in diameter found in mucosa, one containing small eroded arteriole	Death	Dieulafoy [4]
39	♀	Repeated attacks gastric pain, vomiting, hematemesis; in hospital on 3 separate occasions for gastric ulcer; last attack lasted 10 weeks; at autopsy, no obvious sign of disease could be detected in mucosa	Death	Hale White (Lancet 2: 1189, 1906)
42	♀	Recurrent hematemesis 6 years at intervals of about 6 months; vomiting 2 hours after food followed by severe pain for from 1 to 2 hours; tender epigastrium and pain below angle of left scapula; 11 children, 6 living; not markedly anemic and nothing important in history or general condition; 2 small superficial ulcers at cardiac end involving only mucosa and bleeding freely when touched	Complete recovery	Mansell Moullin [19]
42	♂	Five years previously had pain after food vomiting, loss of weight; well until 7 months before admission, when old symptoms recurred with hematemesis and melena; stomach very large; mucous membrane was closely folded on itself and showed area 1½ inches in length from which blood was pouring freely; surface of lesion irregular and covered with granulations; edges well defined but not steep; only mucosa involved; bleeding area infolded and sutured and patient left hospital apparently perfectly well	Complete recovery	Mansell Moullin [19]
31	♀	Continuous dyspepsia with 2 attacks of hematemesis; slight dilatation of stomach with recent erosion at cardiac end; anterior gastrojejunostomy performed; after operation complained of a "slight rather heavy feeling after meals," was ill on an average of once in 3 months but had no hematemesis and general health was better	Recovery	Mansell Moullin [19]

* In this column, ♂ indicates male; ♀, female.

The following list of complaints in diffuse gastric bleeding was brought out by an analysis of fifty-two cases, but this list is typical also of the chief complaints offered by patients in whom the underlying lesion is proved to be a peptic ulcer, cholecystitis, appendicitis, gastrointestinal allergy and a number of other diseases.

Chief Complaints in Fifty-Two Cases of Diffuse Gastric Bleeding

1. Hematemesis, single or recurrent, profuse or moderate, with or without symptoms of shock
2. Gastric pain (cardialgia, gastralgia)
3. Epigastric tenderness
4. Distress after eating (a sense of weight or fulness)
5. Chronic indigestion (one to twenty-five years)
6. Nausea
7. Vomiting

8. Hiccups
9. Flatulence
10. Melena
11. Constipation
12. Headache

ETIOLOGY AND PATHOGENESIS

The stomach is a very busy organ, muscularly, vascularly, nervously and digestively. The magenstrasse, or muscular trough of the lesser curvature along which course food in its passage seems to offer the greatest friction, is the usual situation for local lesions, but in diffuse bleeding the hemorrhage may arise from any part of the stomach. Pringle,[14] in describing hematemesis during attacks of urticaria, said: "The fact that the capillaries of the gastric mucosa form an extremely fine and extensive network supported and separated from the cavity of the organ only by a delicate basement membrane and a single layer of columnar epithelial cells fully accounts for the occurrence of hemorrhage and for its amount in the more severe attacks."

Nevertheless, Hale White concluded that the cause of oozing from an intact gastric wall in the absence of any definite inciting factor is obscure. Since there is no striking increase of blood pressure, the change must be in the walls of the vessels and is local in the stomach as no bleeding takes place at distant parts of the body. Surgeons who have seen the oozing of blood during life have stated that it closely resembles the oozing from the uterus during menstruation. Thompson believed that these cases of diffuse gastric bleeding suggest those of early hemoptysis without discoverable bronchial ulceration and the early hemorrhage of typhoid fever which arises during the congestive stage before the ulcers are well defined; they also resemble the cases of hematemesis that result from congestion in chronic endocarditis and hepatic cirrhosis with portal obstruction, yet no such lesions are found to explain them.

Hood spoke of a section of North Devon where anemia was a common form of illness among the young women. Gastric hemorrhage, in many cases very profuse, frequently accompanied the illness, and the hemorrhage was regarded as a part of the anemia due to the change in the blood. It was noted that in many cases, previous to the hemorrhage, an extreme state of constipation existed, and that the patients made a rapid recovery when treated with iron and sulphate of magnesia. Autopsy was performed in a case in which the hematemesis was fatal, and the wall of the stomach was found to be intact.

One still sees an occasional reference to "vicarious menstruation" in connection with most every type of diffuse hemorrhage. One of the

14. Pringle, J. J.: On a Case of Recurrent Haematemesis with Urticaria, Tr. Clin. Soc. London **18**:143, 1885.

English authors has pointed out that the term "vicarious" is ill advised, because what is meant is simply an extension of the range of the disturbance in the uterus.

It has also been suggested that periodic oozing from the gastric mucosa may be a process of the same kind as that found in cases of epistaxis in which there is a recurrent oozing of blood from the nasal mucous membrane.

In cases in which there is persistent vomiting over a period of many years, the hematemesis is quite probably the result of the vomiting. Aschoff stated that the act of vomiting is introduced by hyperemia of the abdominal organs and particularly of the stomach. Then follows the compression of the abdominal contents by the abdominal musculature, and finally the active contraction of the stomach itself. The pyloric canal is tightly closed while the fundic portion is undergoing the vomiting motions. Consequently, two factors, blood engorgement and spasmodic contraction, act together in producing a venous stasis hyperemia and a venous hemorrhage on the summits of the fold system. That the venous stasis hyperemia, as such, can actually lead to typical hemorrhages and hemorrhagic erosions has been proved by many experiments. Aschoff believed, however, that although venous stasis might be primarily responsible for erosions of the fundus, particularly in vomiting and asphyxia, arterial anemic necroses also might arise from various cramplike conditions of the stomach.

When the hematemesis is due to increased intra-abdominal pressure or to mental excitement, since the patients are normally in good health, one can surmise a constitutional fragility of the walls of the vessels.

In studying his series, Dieulafoy found the case of a man who had never had gastric symptoms but who was taken with sudden severe hematemesis and died. At autopsy, three lesions were found on the lesser curvature of the stomach; the middle one was a fully developed chronic ulcer in the crater of which was a sectioned arteriole completely obliterated by a fibrinous clot. On either side was a superficial erosion, one of which was traversed by a vessel with a lateral opening that was visible with the microscope. Since the entirely sectioned vessel in the old ulcer was obliterated by a clot, it seemed that the fatal hemorrhage came from the vessel traversing the superficial lesion, and Dieulafoy believed that here might be the evolution of a gastric ulcer, in its confirmed state and in the initial stage of a superficial erosion.

Konjetzny,[15] after a minute examination of more than 500 resected specimens, concluded that the typical ulcer of the stomach and duodenum begins as an erosion of the mucosa, and that the erosions are

15. Konjetzny, G. E.: The Inflammatory Basis of the Development of Typical Ulcer of the Stomach and Duodenum, Ergebn. d. inn. Med. u. Kinderh. **38**:184, 1930.

the result of gastritis. Konjetzny believed that in his material there was evidence of all stages of development from the initial erosion to the chronic form, and he distinguished stages of gradual transition between inflammatory erosions and acute ulcer.

Spira [16] has recently pointed out again that there are two distinct forms of ulcer, acute and chronic, which are etiologically independent of each other, and that the exulceratio simplex of Dieulafoy is an acute ulcer showing all the signs of some toxic or acute infective cause. Lesions of this type are uncommon, sudden, virulent, of short duration, fatal or rapidly healing, with no local inflammation and no hyperchlorhydria, and are essentially of systemic origin. In chronic ulcers, the appearance of inflammation is early and persistent; it is present as a preulcerative condition, the ulcer being only an ultimate stage of the mechanism which induces the inflammation and representing the point of its greatest intensity.

Einhorn stated that in the majority of his cases chronic gastric catarrh was probably the cause of the erosions, although at times there might have been some undeterminable factor, and that one would imagine that cases of this type would present a fruitful soil for the development of ulcers. This, however, does not seem to be the case, for in none of these patients was there any justifiable supposition of an existing ulcer during the long course of their illness.

It is well known that chronic gastric ulcers are almost without exception found in the region of the lesser curvature, while the various superficial lesions previously described are all located in the fundus. Aschoff explained that although mucous erosions may occur in any part of the stomach, owing to the anatomic-functional structure the fate of a loss of substance in the mucosa of the gastric pathway must be quite different from that of an erosion of the fundus. The gastric pathway and the pyloric canal may be conceived of as a sort of functional entity with the rest of the stomach representing another entity. The gastric pathway extends from the cardia to the beginning of the pylorus, where it spreads out superficially and goes over into the pyloric canal, and is limited by four taut longitudinal folds of mucous membrane. It possesses its own muscle system and receives its blood supply only through the recurrent branches of the gastric or pyloric arteries. The fundus, on the other hand, receives blood from the arterial branches of the right and left gastric epiploic arteries and also from collateral branches of the gastric artery. Ligations in the region of the gastric epiploic arteries have no recognizable influence on the mucosa of the fundus, while ligations of the gastric or pyloric arteries, or of both vessels, lead to localized nutritional disturbances of the mucosa. Also,

16. Spira, J. Jacques: The Causation of Chronic Gastro-Duodenal Ulcers: A New Theory, London, Oxford University Press, 1931.

the fundus presents a complicated mass of folds in close approximation; the mucosa is much thicker, and by contraction of the muscularis mucosae is made still thicker. The mucosa of the fundus shows a remarkable tendency to produce, through metaplastic processes, a sort of thin mucus which is poured out over the surface of the wound, and there is a greater tendency to epithelization and granulation. It happens, then, that defects in the fundus are quickly covered by a sort of protecting membrane, while defects of the gastric pathway lie bare; in the fundus, there is the greatest mobility of the fold system; in the gastric pathway, there is taut longitudinal stretching; in the former, there is discharge of the gastric juice; in the latter, its reception as by a drainage tube. Therefore, defects along the gastric pathway show a more intense reaction than those in the fundus, continue gaping in a quite different manner, come into contact with gastric juice much longer and are more likely to be injured mechanically by the peristaltic motions than is possible in the region of the fundus, all of which would seem to favor the development of a chronic ulcer. Aschoff stated, however, that all manner of superficial erosions may arise under the influence of disturbed gastric function and concluded that the various anomalies of the gastric mucosa have nothing to do with the typical gastric ulcer, but are the result of the most varied diseases of the stomach.

It seems likely that, even in normal persons, a metabolic upset will cause temporary abrasions of the epithelium or losses of substance in the gastro-intestinal tract, similar to those found in the mucous lining of the mouth, and that ordinarily these heal spontaneously, but, when occurring in the stomach with its intricate structure and great activity, they may at times be more serious. Konjetzny found erosions similar to those in the stomach in parts of the intestinal tract which are inaccessible to the action of the gastric juice.

At present, there is a tendency to consider anaphylaxis or food allergy as a possible cause of gastric disturbances, and it is a question whether gastro-intestinal allergy might not be a factor in the production of some of the conditions under discussion, since where the attacks are recurrent they appear allergic in character. Pottenger [17] explained the anaphylactic state as follows:

> There occurs at times an incomplete elaboration of protein, which results in unmetabolized products gaining access to the blood and lymph streams, from which they are deposited in the skin and mucous membranes. These products possess the property of sensitizing tissues, and particularly of producing their effects upon the parasympathetic neurocellular mechanism. When the substances which have sensitized the cells again come in contact with them a reaction of hypersensitivity occurs. Such a reaction may appear as a vaso-motor rhinitis, an asthma, a hay fever, a

17. Pottenger, F. M.: The Potential Asthmatic, J. Lab. & Clin. Med. **13**:913, 1928.

severe gastro-intestinal disturbance, an urticaria, an eczema, a colloidoclastic reaction, or other syndromes which are less easily recognized. Certain individuals who are prone to this condition seem to possess also a constitutional hepatic inadequacy which is of great importance because of the detoxicating influence of the liver upon substances of alimentary origin. Such individuals show idiosyncrasy to foods and suffer from anaphylactic states more often than those with normal liver function.

Eppinger and Hess [18] expressed the belief that in such patients there is, primarily, a "vagotonic disposition," that is, an abnormal irritability of the parasympathetic nervous system.

In studying the present series of cases, one must agree with these authors that the "neurology of the viscera" is to be considered. A mucous membrane closely folded on itself (case 35, table 1) is regarded as an indication of nervous overactivity; the persistent vomiting, the pylorospasm, the hiccups and many of the other symptoms may be manifestations of a dysfunction of the vegetative system. In this connection, Pottenger stated that nerve action depends on the degree of alkalinity or acidity and on the physical state of the cell and its content, as well as that of the surrounding fluids, in substances such as nutritive materials, cholesterol, hormones and various electrolytes such as calcium, sodium, potassium, phosphate and magnesium. The vagus nerve is closely associated in its action with the potassium of the cell as opposed to the sympathetics, which are linked up in their activity with the calcium of the cell. With a predominance of the vagus, therefore, would go a deficiency of blood calcium with an excess of blood potassium and an increase of blood phosphates. With the present understanding of calcium metabolism, it seems logical to suppose that there is a calcium deficiency in some of these patients.

DIAGNOSIS

The diagnosis of hemorrhage, *per se*, is self-evident, but determining the point of origin of the hemorrhage, whether it is local from an esophageal varix, a peptic or marginal ulcer, a polypus or carcinoma or diffuse bleeding, is always perplexing. The presence of an esophageal varix is usually accompanied by other manifestations of cirrhosis. Carcinoma with its resultant cachexia, anemia and general dissipation of the body integrity is too well known to warrant further discussion. The necrosis and angry congestion of the mucosa provoked by ingestion of poisonous substances, such as mercuric chloride, lye, iodine, etc., need not be discussed. However, polypi may exist without clinical evidence. Patients with gastric ulcers, also, only occasionally produce the famous recurrent symptom-sequence of pain, food, comfort or dis-

18. Eppinger, H., and Hess, L.: Vagotonia: A Clinical Study in Vegetative Neurology, Washington, D. C., Nervous & Mental Disease Publishing Company, 1915.

persion of the pain by alkalis, that is to say, relief when the gastric acid is neutralized and the viscus is moderately filled, which phase is followed by more burning and indigestion when the food passes beyond the area of the ulcer and the alkalinized phase is followed by an acid phase. One must keep in mind the important fact that peptic ulcer may exist and progress even to perforation without symptoms.

Thompson, among a large series of cases exhibiting hematemesis, found three in which there was either no visible pathologic change or diffuse punctate hemorrhage, but no sign of ulcer and no scar. He stated that diagnosis of the exact condition is difficult as between hemorrhage from a circumscribed ulcer, which may be cured by operation, and that from a generally congested mucosa, which may not be so cured. In none of his large series of cases of hematemesis from all causes did the chemical analysis of the gastric contents prove of determining value because the results were too variable, not rarely in the same patient on successive days ranging from anacidity to hyperacidity. Additional difficulty was encountered in the variability and inconstancy of all the so-called "cardinal symptoms" and in the fact that any one symptom, such as pain, vomiting or tenderness which had been present steadily for a long time, might spontaneously disappear or give place to another.

Hale White stated that points that will help in separating cases of diffuse bleeding from those of gastric ulcer are that the former are almost confined to women, the patients are likely to be less wasted than the sufferer from gastric ulcer, and although some give a history of chronic dyspepsia, pain after the ingestion of food and epigastric tenderness, the dyspeptic symptoms are probably less severe. The occurrence of fairly long intervals during which there is no complaint of gastric symptoms is on the whole in favor of diffuse bleeding.

Clerf (personal communication), by gastroscopic examination, observed infiltration and thickening of the mucous membrane with what appeared to be superficial erosions in a case in which there was no definite ulceration; there was slight bleeding from the erosions. Gastroscopy, therefore, may be of use in making a diagnosis, although it has not proved of much practical value.

Principal Diagnostic Factors in Diffuse Bleeding

1. It occurs in young adults (from 20 to 40 years).
2. There is a predominance of females over males (approximately 4:1).
3. The evolution may be silent, or nearly so, with hematemesis the first symptom.
4. The patient may have had good previous health with no gastric symptoms.
5. There may be a period of several months or a year or more between attacks.
6. The condition may be present as a recurrence after operation for gastric or duodenal ulcer.
7. The symptoms are probably less severe than those in cases of true ulcer.
8. The x-ray picture of the gastro-intestinal tract is usually negative.

9. Gastroscopy may be of value in determining the type of lesion.

10. Very often, subsequent to the hemorrhage, all pain and discomfort cease, which could hardly be the case if active ulceration were in progress.

In cases with sudden profuse hematemesis, an immediate differential diagnosis between local or diffuse bleeding of an ulcerating or non-ulcerating process is of secondary importance, except that surgeons would be more hesitant in the presence of diffuse hemorrhage. But, when the underlying pathologic condition is a temporary erosion or a comparatively benign capillary oozing, the general treatment would be different from that in a case of gastric or duodenal ulcer. Smith believed that mucous erosions are common, but that the stomach will heal from erosions as rapidly as the throat will heal from congestion, and that in three or four days the danger is probably past. It is important, therefore, when dealing with gastric bleeding, to keep in mind the various types of conditions that may be present in the mucosa and give rise to alarming hemorrhage, namely: slight catarrhal inflammation, congestion, slight granulation, capillary oozing, petechiae and ecchymoses, abrasions of the epithelium and mucous erosions.

TREATMENT

The treatment for profuse gastric hemorrhage may be divided into three stages. The first stage is the immediate treatment for shock, and since a differentiation between local and diffuse bleeding from the stomach is practically impossible, the therapy for both conditions is the same. The patient must be kept at absolute rest by means of morphine hypodermically, ice being applied to the abdomen and heat to the extremities. The lower bowel should be washed out, and for forty-eight hours no attempt to furnish nutrition should be made. The matter of transfusions is a moot question, as the great majority of gastric hemorrhages cease of their own accord. The red blood count may fall as low as 750,000. It is our practice to type all patients for transfusion promptly, and when the blood count falls below 1,000,000 with the patient's general condition becoming more serious, to give from 300 to 500 cc. of citrated blood.

The various hemostatic serums should be tried, although cessation of bleeding following their use is exceptional rather than the rule. The procedure that stops hemorrhage in one patient may fail in the next. In my experience, a liquid extract of the plant Ceanothus americanus, from 1 to 2 teaspoonfuls three or four times a day, and an extract of Capsella bursa-pastoris, 15 drops three times a day, have most frequently proved effective. Normal horse serum and the patient's own serum in small doses of from 2 to 10 cc. are at times effective.

Soper,[19] in a recent article, advocated the treatment of gastric hemorrhage by the retention catheter introduced intranasally. The stomach is lavaged with cool tap water by means of a large glass piston syringe, and the tube is left in the stomach in order that a recurrence of the bleeding may be immediately detected and all acid secretions withdrawn. On the fifth day, the tube may be allowed to pass down into the duodenum and a high caloric mixture of milk, egg and lactose given, with gelatin water and egg albumin water by mouth.

Operative intervention would appear to be an unwise procedure at this stage; Mayo Robson stated that the treatment of parenchymatous or capillary hemorrhage by any surgical method would seem to be of doubtful value. A limited personal experience and information obtained from the literature point to the conclusion that mechanical interference is not of necessity fatal, but it is agreed that the patients stand a better chance of recovery without rather than with operation.

After the bleeding has stopped, attention to the nutrition and elimination is indicated. Duodenal feedings for several days through the Jutte tube have proved invaluable in tiding the patients over a precarious period when the margin between success and failure in the establishment of substantial up-building is so narrow.

In cases in which it seems likely that the bleeding has been diffuse rather than from a chronic circumscribed ulcer, the subsequent treatment should be administered, keeping in mind that many of the lesions heal spontaneously and that an excessive use of drugs in general should be avoided. Adequate nutrition, with liver extract and iron to stimulate blood regeneration, is essential. All foci of infection should certainly be removed, and the patients may with wisdom avoid undue physical and mental strain. Adequate periods of rest are splendid for recuperation.

When indicated, atropine, from 1/200 to 1/50 grain (0.00032 to 0.0013 Gm.), three times a day, may be given to minimize the gastric acidity and also to counteract any tendency to pyloric spasm. Yet it has been stated[7] that all artificially produced defects in the gastric mucosa heal less quickly in the presence of atropine therapy, doubtless due to the loss of tone of the whole stomach. Colloidal hydrate of aluminum rather than sodium bicarbonate should be given to neutralize excess acid, since the former does not produce a subsequent hyperacidity. Calcium gluconate, from 10 to 30 grains (0.65 to 1.95 Gm.), three times a day by mouth, and parathormone injected subcutaneously twice weekly are valuable when there is a calcium deficiency, and finally the patients should have proper sedation for neurosis in the form of elixir of phenobarbital and elixir of bromide combined.

19. Soper, H. W.: The Treatment of Hematemesis by the Retention Catheter, J. A. M. A. **97**:771 (Sept. 12) 1931.

SUMMARY

Serious gastric hemorrhage may occur from any part or all of the gastric mucosa either in patients who have had an irrelevant history and have apparently been well until a serious attack of hematemesis occurred, or in those who have suffered periodically from indigestion. Cases have been cited in which the gastric bleeding appeared to result from factors such as an increased abdominal tension, emotional strain, vagotonia, allergies, anemia, etc.

A differential diagnosis may be impossible, and in the majority of cases the diagnosis made before operation has been bleeding ulcer.

The treatment should be along medical rather than surgical lines, since hemorrhage of a diffuse kind arising from the gastric mucosa does not appear amenable to surgical approach. Support, elimination and rest are the cardinal features in the management of these cases.

USE OF LIVER EXTRACT INTRAVENOUSLY

REPORT OF TEN CASES

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Castle and Taylor [1] have recently shown that maximal responses of reticulocytes were obtained in the treatment of patients with pernicious anemia, during relapse, when the amount of liver extract derived from 100 Gm. of liver was administered intravenously. The solution suitable for intravenous injection was prepared by dissolving approximately 4.5 Gm. of a commercial preparation of fraction G [2] (liver extract) in physiologic solution of sodium chloride after washing the extract in ether. The solution was then filtered or centrifugated, sterilized by boiling for five minutes and made so that 20 cc. contained the amount of material derived from 100 Gm. of whole liver.

In studying the nature of the active principle in liver, Cohn [3] and West [4] and their respective associates had previously prepared highly purified fractions of liver which were suitable for intravenous injection and which were found to be potent. The practical application of these fractions was precluded because of the technical difficulties involved in their preparation and because of the large amounts of whole liver required (from 25,000 to 8,000 Gm.).[3]

The maximum reticulocyte responses produced by these highly purified fractions were no greater than those obtained from a single intravenous injection of an amount of liver extract derived from 100 Gm. of liver; therefore, Castle and Taylor demonstrated that there was a great loss in potency resulting from the subsequent stages of

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1. Castle, W. B., and Taylor, F. H. L.: Intravenous Use of Extract of Liver, J. A. M. A. **96**:1198 (April 11) 1931.

2. Cohn, E. J.; Minot, G. R.; Fulton, J. F.; Ulrichs, H. F.; Sargent, F. C.; Weare, J. H., and Murphy, W. P.: The Nature of the Material in Liver Effective in Pernicious Anemia, J. Biol. Chem. **74**:lxix (July) 1927.

3. Cohn, E. J.; McMeekin, T. L., and Minot, G. R.: The Nature of the Substance Effective in Pernicious Anemia, Tr. A. Am. Physicians **45**:343, 1930.

4. West, Randolf, and Howe, Marion: Liver Fractions in Pernicious Anemia, J. Clin. Investigation **9**:1, 1930.

chemical purification. Also, the reticulocyte responses produced by 100 Gm. of liver extract given intravenously were as great as those obtained when large doses of liver extract no. 343, N. N. R., were given in single or divided doses. That there was a defective absorption of the active principle contained in liver from the intestinal tract seems to be clearly demonstrated by them. They suggest that the strikingly greater effectiveness of the active principle when administered intravenously is possibly of some significance in the etiology of the disease and indicates that there may be a defect in the absorption of the hematopoietic factors contained in the food ingested.

More recently, Strauss, Taylor and Castle [5] have obtained satisfactory reticulocyte responses when a preparation similar to the one previously described was administered intramuscularly. Working independent of Castle and his associates, Prof. M. Gänsslen [6] has reported similar results following the daily intramuscular injection of a liver extract.

A preparation suitable for injection purposes and made from liver extract no. 343, after the method employed by Castle and his associates (as previously described), has been used intravenously by us in the treatment of ten patients. Seven of the patients had typical pernicious anemia, and six of these had been under observation and treatment with liver extract no. 343, administered orally, over a period of time ranging from six months to four years. Previous reticulocyte responses in certain of these patients, with essentially little variation in the potency of the material throughout, afford useful information in comparing the effectiveness of liver extract no. 343 when administered orally and when injected intravenously. The remaining three cases of anemia resembled hemolytic jaundice; however, the characteristics of the red blood cells and the other observations on the blood, except for the persistently high reticulocyte counts, could not be differentiated from those in pernicious anemia during relapse.

TECHNIC AND EFFECTS OF INJECTION

After a sufficient control period, the patients received, at a single injection, 20 cc. of liver extract (the amount derived from 100 Gm. of liver). The usual daily observations of the blood were made, and injections were given at regular weekly intervals, unless some definite contraindication arose.

5. Strauss, M. B.; Taylor, F. H. L., and Castle, W. B.: Intramuscular Use of Liver Extract, J. A. M. A. **97**:313 (Aug. 1) 1931.

6. Gänsslen, M.: Ein hochwirksamer, injizierbarer Leberextrakt, Klin. Wchnschr. **9**:2099 (Nov. 8) 1930.

The liver extract was brought to body temperature before injection. During and immediately following each injection the patient was observed closely for the occurrence of a reaction, and the blood pressure was taken and recorded at intervals of one minute. The rate of injection ranged from 0.5 to 2 cc. per minute, depending on the response of the patient.

There were a generalized flush to the skin and a sensation of excessive heat in all the patients during the time of the injection. Ninety-five injections were given, and chills were noted following five of these. Four of the chills followed the initial injection, and the fifth on a second injection. All of the chills were mild and lasted about fifteen minutes. The blood pressure decreased slightly at some time during the injection in essentially all patients, but rapidly returned to its original level. The average decrease in the systolic blood pressure during the ninety-five injections was 26 mm. of mercury, and the average decrease in the diastolic blood pressure, 16 mm. At no time did the systolic blood pressure fall below 80. Slight increases in blood pressure were observed in a few instances during the process of injection. Three patients (cases 1, 5 and 7) always had slightly labored respirations during the injections, and in one instance precordial pain was noted when the blood pressure fell. Nausea, vomiting and abdominal cramps rarely occurred. The urine voided following the injections was usually dark amber in color, but no casts, red blood cells or increase in albumin were observed.

While none of the reactions was of a serious character, the slow administration of the substance is recommended.

REPORT OF CASES

CASE 1.—This patient was a white woman, aged 50, married, who had hemolytic jaundice. She had a severe macrocytic anemia which could not be differentiated from that of pernicious anemia during relapse, except for a persistent reticulocytosis. Both the spleen and liver were markedly enlarged and firm. There were no evidences of neurologic involvement; the temperature fluctuated, with daily rises to 101 F.; the blood bilirubin content was 1 mg. per hundred cubic centimeters, and a definite icterus of the skin and sclerae was present. Free hydrochloric acid in the gastric contents was absent following the administration of histamine. A typical blood response and rapid clinical improvement followed the injection of liver extract intravenously.[7] The red blood cells reached a normal level after seven injections of liver extract, as is clearly shown in chart 1. A maximal reticulocyte response, reaching 624,000 per cubic millimeter of blood (47.5 per cent), was obtained in the presence of a fever, followed by a normal temperature. Secondary rises in the reticulocytes were observed four days after the second and third injections, respectively, even though the initial reticulocyte response appeared to be maximal.

7. Unless otherwise mentioned, each intravenous injection of 20 cc. contained the amount of active principle derived from 100 Gm. of liver.

Case 2.—A white woman, aged 31, with hemolytic jaundice entered the hospital with essentially the same clinical and laboratory picture as that recorded in case 1. She had been under observation for a year; when she first entered the hospital, one year before, she was in a state of relapse, jaundiced and critically ill. She was given both liver extract no. 343 and ventriculin by mouth, at separate periods, with an unsatisfactory reticulocyte response following both. On the continued administration of liver extract derived from 300 Gm. of liver daily, the red blood

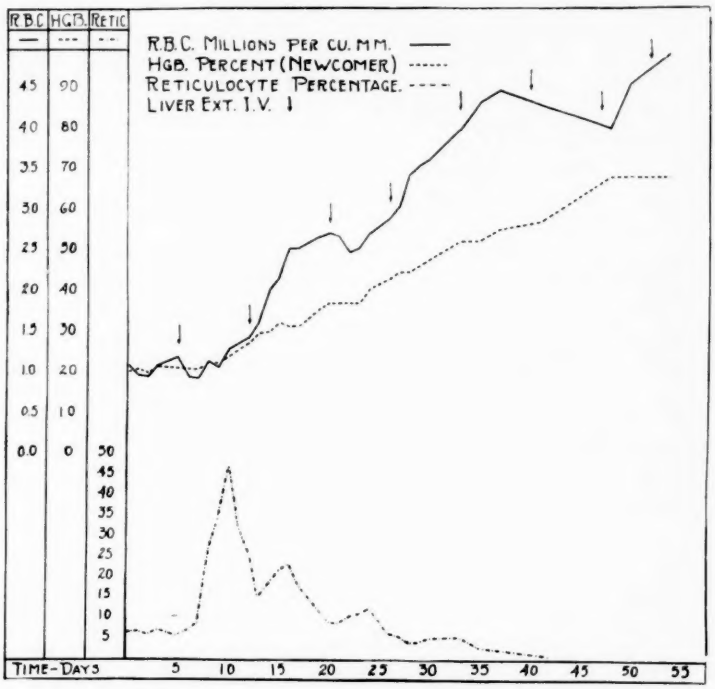

Chart 1.—Response of the red blood cells, hemoglobin and reticulocytes in a patient (case 1) with hemolytic jaundice to liver extract given intravenously. (Extract derived from 100 Gm. of liver given at each injection.)

cells eventually reached normal, remaining at a level of approximately 4,500,000 per cubic millimeter of blood until two months prior to the patient's present entry into the hospital.

During the period of two months previous to her present admission, the red blood cells dropped from 4,500,000 to 1,600,000 per cubic millimeter of blood, despite the daily administration of liver extract derived from 400 Gm. of liver. On admission, the patient was given two blood transfusions of 500 cc. each, liver extract derived from 600 Gm. of liver daily for thirty days, and 0.18 Gm. of metallic iron (iron and ammonium citrate) daily for fourteen days, without a satisfactory response of the red blood cells. When liver extract derived from

75 Gm. of liver was given intravenously, there was a very satisfactory response of the reticulocytes and a marked improvement occurred in the patient's clinical condition (chart 2).

Castle and Taylor [1] reported the case of a patient with pernicious anemia who failed to respond to the daily oral administration of liver extract derived from 300 Gm. of liver over a period of ten days, but

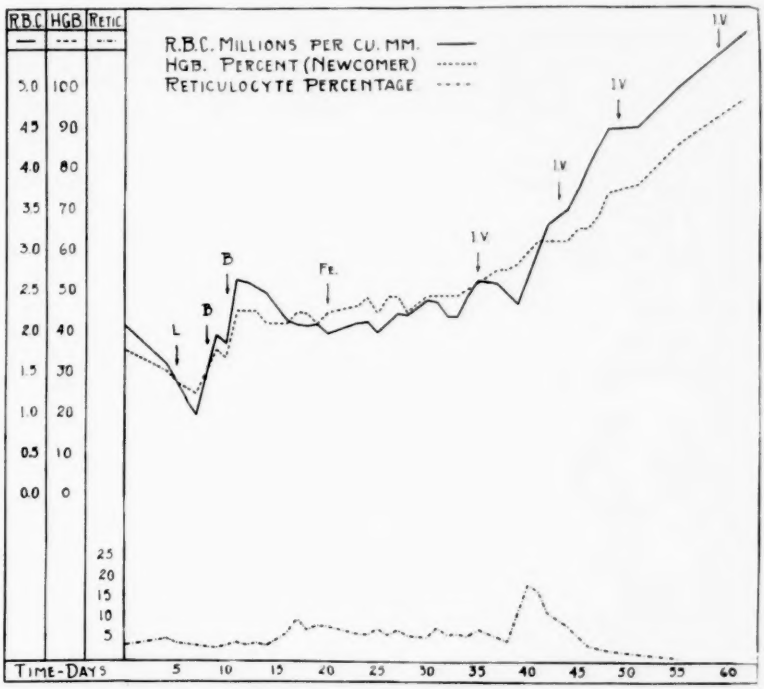

Chart 2.—Response of red blood cells, hemoglobin and reticulocytes of a patient (case 2) with hemolytic jaundice to: (*L*) liver extract no. 343 derived from 600 Gm. of liver daily; (*B*) a blood transfusion of 500 cc. of whole blood; (*Fe.*) 0.18 Gm. of metallic iron (iron and ammonium citrate) daily; (*I.V.*) liver extract given intravenously in amounts of 15, 5, 20 and 8 cc., respectively (20 cc. was derived from 100 Gm. of whole liver).

who did respond to a single intravenous injection of liver extract derived from 100 Gm. of liver.

Case 3.—A white man, aged 54, with a typical case of pernicious anemia, had two distinct relapses that responded to liver extract no. 343 and one relapse that responded to ventriculin, 30 Gm. daily. The maximum reticulocyte response following the administration of ventriculin reached 47 per cent (absolute number,

643,000 per cubic millimeter of blood) at an initial level of 1,340,000. The red blood cell count reached a normal level and remained there for six months. During the next seven months the red blood cell count remained below 4,000,000, even though the patient took the amount of liver extract derived from 300 Gm. of liver daily during the entire thirteen months.

Liver extract derived from 100 Gm. of liver was given intravenously at an initial level of 3,650,000 red blood cells per cubic millimeter, and a reticulocyte response of 5.6 per cent was obtained. After five intravenous injections, the red blood cell count reached 5,430,000 and the hemoglobin content 101.2 per cent.

CASE 4.—This patient was a white woman, aged 59, married, who entered the hospital recently because of cardiac failure. She had a typical case of pernicious anemia and had been under observation since October, 1927. During this period she had had frequent relapses because of the voluntary omission of liver extract therapy. Seven definite reticulocyte responses were obtained, as recorded in the accompanying table. Except in one instance, the absolute number of reticulocytes resultant from one injection of liver extract was greater than any of the reticulocyte responses obtained when liver extract was given by mouth, even though

The Height of the Reticulocyte Responses Following Varying Amounts of Liver Extract by Mouth and One Intravenous Injection of Liver Extract in the Same Patient (Case 4)

Date Treatment Began	Liver Extract Derived from Gm. Liver	Day of Reticulocyte Peak	Reticulocytes, per Cent	Red Blood Cells per C.Mm.	Hemoglobin (Newcomer), per Cent	Absolute Number of Reticulocytes, per C.Mm. at Peak
1/ 7/28	600 daily	6	25.9	1,270,000	29.4	328,000
10/ 8/28	300 daily	10	6.6	1,800,000	45.3	118,800
11/22/28	300 daily	8	14.3	2,250,000	49.6	321,000
1/ 4/30	300 daily	6	18.7	2,110,000	44.6	394,570
2/10/30	300 daily	5	13.8	1,820,000	44.6	251,160
8/11/30	300 daily	5	8.5	2,440,000	41.6	251,160
6/27/31	100 intravenously	4	11.2	3,250,000	65.5	364,000

the initial red blood cell level was above 3,000,000. Within three weeks after the initial injection of liver extract, the red blood cell count had reached 4,750,000 per cubic millimeter.

CASE 5.—A white man, aged 48, married, who had typical pernicious anemia, entered the hospital while recovering from bronchopneumonia and during a severe relapse. Chart 3 shows the magnitude of the hematopoietic response to the first and subsequent injections of liver extract.

CASE 6.—A white woman, aged 71, with typical pernicious anemia complicated by a severe chronic nephritis, first entered the hospital in August, 1927. A reticulocyte response of 49.4 per cent was obtained at an initial level of 840,000 red blood cells, when liver extract derived from 400 Gm. of liver was given daily. Since that time the patient had taken liver extract derived from 200 to 300 Gm. of liver daily. She entered the hospital recently because of gross hematuria and an acute exacerbation of a chronic nephritis. The blood nonprotein nitrogen was high, but after it returned to normal, the patient was given liver extract intravenously, when the red blood cells were at a level of 3,670,000 per cubic millimeter. The reticulocytes increased to 4.4 per cent, which was followed by a rise in the red blood cells to 4,300,000 within three weeks' time.

CASE 7.—A white man, aged 55, with typical pernicious anemia, entered the hospital because of acute progressive neurologic changes, accompanied by a rather

severe diarrhea and a sore tongue. This patient had been under our observation for six months and had taken regularly the amount of liver extract derived from 300 Gm. of liver daily. The red blood cell count during that time had been maintained at a level of approximately 4,500,000, but, on the patient's entrance to the hospital, it was found to have decreased to 3,970,000. Injections of liver extract were given for four consecutive weeks with no increase in reticulocytes or red blood cells, but the patient improved symptomatically. Subsequently, two injections weekly were given for a period of seven weeks, after which time the number was reduced to one per week. Although the response of the patient to

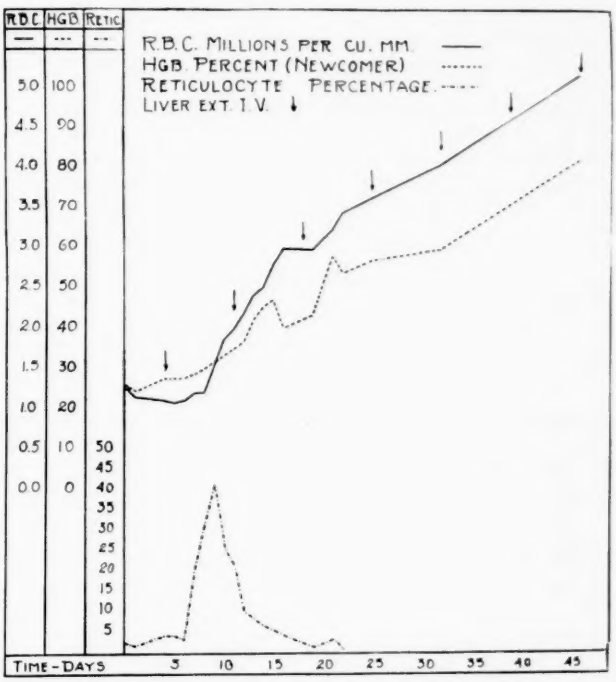

Chart 3.—Effect on red blood cells, hemoglobin and reticulocytes when liver extract derived from 100 Gm. of whole liver was given intravenously at weekly intervals to a patient (case 5) who had pernicious anemia.

liver extract given intravenously was slow, requiring four months for the red blood cells to reach 5,000,000, the count has been maintained approximately at this level for four months.

Case 8.—This patient, a white woman, aged 55, with typical pernicious anemia and marked cord changes, entered the hospital during her third relapse. She had not taken liver extract or liver for two years until approximately three weeks prior to her entry to the hospital. During the three weeks, she took liver extract derived from 8,300 Gm. of liver and, consequently, had improved clinically. The red blood cells numbered 2,720,000; the hemoglobin amounted to 57.3 per cent

and the reticulocytes to 0.8 per cent. Apparently the patient had had a reticulocyte response resulting from the liver extract ingested, and, as a result, there was only a slight increase in reticulocytes (4 per cent) following one injection of liver extract intravenously. After four injections of liver extract the red blood cells reached approximately a normal level.

CASE 9.—A white woman, aged 55, with typical pernicious anemia, was first treated with liver extract during a relapse in April, 1929. The red blood cells at that time numbered 1,100,000, and the patient was given the amount of extract derived from 600 Gm. of liver daily. The maximum reticulocyte peak reached was 28 per cent (487,200 was the absolute number of reticulocytes). After the red blood cells reached normal, the amount of extract derived from 300 Gm. of liver was sufficient to maintain a red blood cell level of approximately 4,500,000, although the patient had had acute attacks of pyelitis frequently since November, 1929.

During the six months prior to her present admission to the hospital she failed to report for examination; the spinal cord signs and symptoms progressed, and the red blood cells decreased to a level of 2,190,000. Although she had a low grade fever, resulting from an acute exacerbation of a chronic cystitis and pyelitis, a reticulocyte response of 17.5 per cent (absolute number of reticulocytes, 382,700) was obtained on the fifth day, following one intravenous injection of liver extract. After three injections, the red blood cell count reached 4,150,000.

CASE 10.—A white man, aged 27, entered the Methodist Hospital in June, 1929, complaining of loss of weight, diarrhea, weakness, palpitation and swelling of the ankles. On physical examination he was markedly jaundiced, emaciated and mentally depressed. The spleen was enlarged, and there was considerable edema of the ankles. There were no evidences of cord involvement. The red blood cell count was 1,280,000 per cubic millimeter, with hemoglobin 24 per cent and reticulocytes 0.8 per cent. The blood smears were not distinguishable from those of pernicious anemia during relapse. Free hydrochloric acid was present in the gastric contents.

The patient was given the amount of liver extract no. 343 derived from 300 Gm. of liver daily. Unfortunately, no reticulocyte counts were made during the early course of his treatment; however, after four months' time, the red blood cell count reached 4,940,000, the hemoglobin content was 83.3 per cent, and there was a striking clinical improvement in the patient. Liver extract therapy was then voluntarily omitted, and, after two months' time, the signs and symptoms that were present on the patient's admission returned, and the red blood cell count decreased to 2,240,000 per cubic millimeter.

On resuming liver extract therapy, he improved clinically, and the red blood cell count reached 4,390,000 within three months' time. The red blood cell counts were maintained at essentially normal levels for a period of ten months, and during this time the patient continued to take the amount of extract derived from 300 to 400 Gm. of liver daily. However, for no apparent reason, his red blood cells decreased to 2,400,000 during the ensuing two months. On admission to the outpatient department, he was given one injection of liver extract intravenously, and on the fifth day of treatment the reticulocyte count reached 13.2 per cent (absolute number of reticulocytes, 403,900). Within thirty-nine days, the red blood cell count was 5,090,000, and the hemoglobin 91.7 per cent. The injections of liver extract were then discontinued, and the patient received daily, by mouth, the amount of liver extract no. 343 derived from 300 Gm. of whole liver. Within four months he had another relapse, the red blood cells reaching a level of

1,730,000 and the hemoglobin 37.3 per cent. Following one intravenous injection of liver extract the reticulocytes reached a peak of 26.6 per cent.

The diagnosis in this case is not clear, although the clinical features resemble those of hemolytic jaundice more than those of pernicious anemia.

COMMENT AND SUMMARY

The preparation of a solution of liver extract no. 343, after the method described by Castle and Taylor, has been found to contain the active principle in liver effective in the treatment for pernicious anemia and suitable for intravenous administration.

The potency of a small amount of liver extract administered intravenously, as reported by Castle and Taylor, has been fully confirmed by our results in the treatment of seven patients with pernicious anemia and three patients with hemolytic jaundice. Cases 2, 3, 4, 9 and 10 also illustrate that small amounts of liver extract, given intravenously, have been effective in patients whose red blood cells were not maintained at normal levels, although the amount of potent extract derived from 300 to 600 Gm. of liver had been given daily, by mouth, over a period of time. This suggests, as Castle and Taylor pointed out in their paper, that there is possibly a defective absorption of the active principle from the gastro-intestinal tract in such cases. It would also seem, from our experience and from that of others, that there is a considerable variation in individual patients and in the same patient in this respect. While it is definitely known that most therapeutic agents are much more effective when given intravenously than when given by mouth, it would appear that, in the case of liver extract, the difference in potency cannot be accounted for entirely by this variation. In the presence of persistent diarrhea, nausea and vomiting and in the treatment of certain fastidious patients, the intravenous method of administration should also be of considerable value.

It is generally known [8] that, in the presence of infectious processes, fever and intoxication, liver extract given by mouth has been relatively ineffective. Cases 1 and 9 show that liver extract administered intravenously was highly efficacious in the presence of fever.

One of us treated three patients with pernicious anemia in whom, while sufficient amounts of liver extract were taken by mouth, acute progressive spinal cord changes developed, accompanied by a severe anemia that did not respond to very large daily amounts of liver extract.

8. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. A. M. A. **89**:759 (Sept. 3) 1927. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy, Am. J. M. Sc. **175**:581 (May) 1928. Smithburn, K. C., and Zerfas, L. G.: The Inhibitory Action of Infection and Fever on the Hematopoietic Response in a Case of Pernicious Anemia, Ann. Int. Med. **4**:1108 (March) 1931.

It is probable that, under such circumstances, liver extract administered intravenously would have been of great value.

In cases 3, 4 and 6, in which the initial red blood cell levels were 3,650,000, 3,250,000 and 3,670,000 per cubic millimeter, respectively, slight but distinct reticulocyte rises were obtained following the intravenous administration of extract derived from 100 Gm. of liver. This is in contrast to the absence of reticulocyte responses reported by Minot,[9] one of us (Dr. Zerfas[10]) and others when large amounts of potent fractions of liver were given daily by mouth to patients whose initial red blood cell counts were much above 3,000,000.

Although the reticulocyte peak is reached sooner when liver extract is given intravenously than when it is given orally, we do not believe that its use alone will suffice in patients who are desperately ill. It would appear, however, that the intravenous use of liver extract supplementary to blood transfusions is indicated in this type of case.

Two cases of hemolytic jaundice (cases 1 and 2), with severe macrocytic anemia, showed maximal reticulocyte responses following one intravenous injection of liver extract; a third case (case 10), possibly one of hemolytic jaundice, responded in a similar manner.

While we believe that the intravenous administration of liver extract will not supplant its use by mouth, we are convinced that its supplementary use, intravenously, will be of distinct benefit in the therapy of pernicious anemia and possibly in other macrocytic anemias.

NOTE.—Since submitting this paper for publication, twenty-five additional patients with primary pernicious anemia have been treated with liver extract administered both intramuscularly and intravenously, making a total of five hundred injections. In every instance the clinical improvement and the hematologic response have been as striking as in the ten cases here reported.

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9. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract, Am. J. M. Sc. **175**:599 (May) 1928.

10. Zerfas, L. G.: Liver Extract in Pernicious Anemia, Arch. Int. Med. **47**: 135 (Jan.) 1931.

VARIATIONS IN THE TOTAL BLOOD LIPID IN ALIMENTARY LIPEMIA

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The present investigation was conducted in an attempt to determine whether in the absence of pancreatic or hepatic disease the concentration of the total blood lipid at fixed intervals after the ingestion of a large amount of fat adhered to a typical pattern. If a typical curve were demonstrated, a method similar to the dextrose tolerance test could then be employed to discover what modifications were produced by such disease. The total blood lipid was chosen as an indicator of lipolytic activity largely because it could be estimated by a relatively simple method requiring only small amounts of blood.

METHOD

The procedure was as follows: After a twelve hour fast, a specimen of blood was withdrawn. The subject immediately thereafter drank 100 cc. of olive oil. Samples of blood were then taken two, three, four, five and six hours after the ingestion of the oil. In many instances, the fifth hour determination was omitted, while in a small number a seventh hour specimen was added.

The total alcohol ether extract was determined by a method developed by Bernhard in the Achelis laboratory. A strip of fat-free filter paper (Whatman no. 100, fat-free, for milk analysis) measuring about 160 mm. was cut in half lengthwise. It was then impregnated with 1 cc. of whole blood, spread out in such a manner that it occupied about seven eighths of the length of the paper. After air-drying for one-half hour, it was folded in a manner similar to a folded filter, and placed in a Folin sugar tube to which was added 4 cc. of a mixture of equal parts of 95 per cent ethyl alcohol and pure ether. A condenser was placed in the Folin tube, and the mixture allowed to reflux for one hour on a slow boiling water bath. (During the extraction, care must be exercised that the alcohol ether mixture does not evaporate below 3 cc.) The condenser was then removed and the extract transferred to a weighed porcelain crucible. The Folin tube was washed four times with 5 cc. portions of alcohol ether, and the washings were added to the crucible. The extract, with the added washings, was evaporated on the water bath and the crucible then placed in a desiccator for two hours and weighed on the Bunge microbalance. All determinations were made in duplicate. As I was interested in comparative curves, estimations of the various fractions of the total lipid were considered unnecessary in the present study. Many such estimations

From the service of Dr. Packard at the Gouverneur Hospital and the Achelis Laboratory of the Lenox Hill Hospital.

were performed, however, during the course of the work, and the variations in the cholesterol and lipoid phosphorus were found to be so slight that their effect on the curve could be disregarded.

To establish normal figures with these technical procedures, the test was performed on sixty-seven patients grouped as follows: group A, seventeen healthy men received through an employment agency, and group B, fifty patients (forty-six men and four women) afflicted with a variety of illnesses, patients with pancreatic (including diabetes mellitus) or liver disease being excluded as carefully as the present methods would permit. In those suffering from an acute infectious disease the examination was made after at least a week of convalescence, and in the cardiac group, after compensation was restored. During the test, those in group A were ambulatory, while the majority in group B were confined to bed.

TABLE 1.—*Variation in the Total Blood Lipid in Seventeen Normal Men Following the Ingestion of Olive Oil*

				Total Lipid, Mg. per 100 Cc.					
Case	Patient	Sex	Age	Fasting	2 Hrs.	3 Hrs.	4 Hrs.	5 Hrs.	6 Hrs.
1	N. I.	M	21	820	860	820	840	870	860
2	S. T.	M	22	720	620	620	870	880	880
3	R. O.	M	23	850	940	850	800	940	980
				860	950	870	820	920	980
4	W. H.	M	22	870	1,070	920	810	890	...
5	L. E.	M	24	840	880	920	950	970	1,000
6	I. I.	M	25	840	880	950	1,060	1,020	970
7	I. H.	M	27	920	980	940	810	910	1,040
8	G. A.	M	28	840	830	860	800	900	860
9	S. R.	M	30	660	720	730	780	790	720
10	S. M.	M	30	840	830	830	780	820	880
11	S. H.	M	33	660	740	750	780	770	850
				660	720	740	720	700	880
12	S. E.	M	34	900	...	940	900	1,010	1,000
13	E. L.	M	35	830	940	1,000	1,000	1,050	920
				840	940	1,030	1,030	960	860
14	S. W.	M	35	840	...	930	610	550	840
15	D. I.	M	37	1,010	...	1,070	1,100	980	1,010
16	L. U.	M	40	1,120	1,100	1,030	1,000	1,000	1,030
17	H. O.	M	48	850	980	1,000	940	1,010	920
Maximum				1,120	1,100	1,070	1,100	1,050	1,040
Average				844	881	890	874	895	909
Minimum				660	620	620	610	550	720

After a lapse of several days or weeks, the test was repeated in five cases; in two, additional tests were performed to ascertain the effect of starvation and the ingestion of 100 Gm. of dextrose on the blood lipid curve.

COMMENT

Analysis of the figures presented in tables 1 and 2 shows that, following the drinking of 100 cc. of olive oil, the variations in the total blood lipid, instead of adhering to a single typical pattern, fall into three main types which I have arbitrarily termed the ascending, flat and descending. Considering a rise of 100 mg. or more as significant, 63.2 per cent of the patients gave an ascending, 17.5 per cent a flat and 19.3 per cent a descending type of curve. It is interesting to note that Rohdenburg, Bernhard and Krehbiel [1] performed the dextrose tolerance

1. Rohdenburg, G. L.; Bernhard, A., and Krehbiel, O.: A Study of Sugar Mobilization Based upon 228 Human Cases, Am. J. M. Sc. **159**:577, 1920.

TABLE 2.—*Variations in the Total Blood Lipid in Fifty Patients Following the Ingestion of Olive Oil*

Case	Patient	Sex	Age	Total Lipid, Mg. per 100 Cc. Fasting	2 Hrs.	3 Hrs.	4 Hrs.	5 Hrs.	6 Hrs.	7 Hrs.	Diagnosis
1	W. R.	M	23	730	900	1,040	995	1,010	1,020	.....	Influenza
2	M. E.	M	25	960	1,100	1,050	1,070	1,090	870	.....	Lobar pneumonia
3	A. C.	M	25	930	910	920	930	950	980	.....	Acute rheumatic fever
				1,040	1,000	1,060	1,110	1,110	1,040	.....	
4	H. Mc.	M	26	1,060	1,060	990	960	.....	900	.....	Lobar pneumonia
5	P. M.	M	26	1,060	1,160	1,030	1,140	.....	1,050	.....	Influenza
6	H. S.	F	27	1,130	1,210	1,230	1,210	1,200	1,180	.....	Acute rheumatic fever
7	S. L.	M	31	1,040	1,100	1,120	1,210	.....	1,310	.....	Lobar pneumonia; postencephalitic paralysis agitans
8	N. M.	M	32	1,200	1,370	1,100	1,090	.....	1,100	.....	Acute infectious arthritis
9	J. C.	M	34	780	850	880	810	820	830	.....	Submersion; bronchopneumonia
10	J. M.	F	34	1,020	1,150	1,160	1,195	.....	1,100	.....	Chronic endocervicitis
11	O. L.	M	35	910	1,000	1,010	1,065	.....	920	.....	Gastric ulcer
12	M. P.	M	37	940	890	850	855	.....	770	.....	Acute arthritis
13	C. L.	M	37	1,090	1,190	.....	1,460	1,480	1,200	.....	Acute bronchitis
14	B. C.	M	38	1,010	1,110	1,120	1,010	.....	920	.....	Acute rheumatic fever
15	A. Z.	M	40	990	1,010	1,130	1,170	.....	1,120	.....	Chronic valvular disease
16	D. C.	M	40	950	1,100	1,025	1,220	.....	980	.....	Psychoneurosis
17	J. B.	M	41	1,010	1,240	1,220	1,240	.....	1,470	.....	Lobar pneumonia
18	L. F.	M	42	870	860	950	1,005	1,310	1,130	1,010	Influenza
19	J. D.	M	42	990	1,110	1,110	1,245	.....	1,200	.....	Carbon monoxide poisoning
20	W. T.	M	43	750	800	805	1,020	.....	1,000	.....	Sacro-iliac arthritis
21	P. M.	M	42	1,030	1,120	1,150	1,010	.....	1,160	.....	Lobar pneumonia
22	H. S.	M	43	960	1,100	1,240	1,130	.....	1,200	.....	Alcoholism; submersion
23	A. M.	M	48	740	760	820	1,010	.....	1,150	.....	Lobar pneumonia
24	D. P.	M	49	810	823	1,450	1,035	1,060	.....	.....	Influenza
25	J. N.	M	50	850	860	940	1,150	.....	1,000	.....	Carbon monoxide poisoning
26	J. L.	M	53	840	940	940	950	1,020	1,120	.....	Sciatica
27	R. W.	M	53	860	790	1,080	1,030	.....	1,040	.....	Dextrocardia; alcoholism; starvation
28	G. S.	M	54	1,120	1,150	1,260	1,125	1,280	1,490	.....	Syphilis; Charcot knee
29	J. A.	F	54	950	900	1,040	1,310	.....	1,190	.....	Neurosis
30	P. M.	M	40	1,100	1,180	1,120	1,175	.....	1,040	.....	Influenza; chronic nephritis
31	G. S.	M	42	1,160	1,100	1,060	1,000	1,000	1,060	.....	Chronic nephritis
32	A. B.	M	44	1,065	1,080	970	1,000	.....	1,110	.....	Gastric ulcer; unresolved pneumonia; marked arteriosclerosis
33	J. Z.	M	45	1,090	1,180	1,180	1,100	.....	1,210	.....	Arteriosclerosis; hemiplegia
34	W. Z.	M	46	990	1,000	930	820	950	1,020	.....	Arteriosclerotic nephritis; emphysema
35	H. G.	M	48	1,260	1,350	1,280	1,120	.....	1,540	.....	Coronary sclerosis; auricular fibrillation
36	H. S.	M	50	990	1,100	985	1,030	1,080	1,120	.....	Moderate arteriosclerosis; myocardial degeneration
37	J. D.	M	50	1,070	1,200	1,080	1,035	.....	1,100	.....	Moderate arteriosclerosis; influenza
38	H. C.	M	51	1,020	1,010	1,100	1,095	.....	1,120	.....	Arteriosclerosis; chronic bronchitis and emphysema
39	S. S.	M	52	1,000	970	1,000	920	.....	940	.....	Chronic nephritis
40	L. Z.	F	54	1,040	1,220	1,420	1,310	.....	1,340	.....	Arteriosclerotic nephritis
41	A. R.	M	55	1,080	870	845	935	890	760	900	Chronic nephritis
42	F. B.	M	56	1,070	.....	1,070	1,033	1,144	1,218	895	Arthritis deformans; moderate arteriosclerosis
43	J. K.	M	59	1,580	1,490	1,255	1,170	1,080	.....	960	Marked arteriosclerosis; cerebral thrombosis; coronary sclerosis
44	A. P.	M	60	1,180	1,330	1,320	1,300	.....	1,200	.....	Arteriosclerotic heart disease

TABLE 2.—*Variations in the Total Blood Lipid in Fifty Patients Following the Ingestion of Olive Oil—Continued*

				Total Lipid, Mg. per 100 Cc.							
Case	Patient	Sex	Age	Fasting	2 Hrs.	3 Hrs.	4 Hrs.	5 Hrs.	6 Hrs.	7 Hrs.	Diagnosis
45	P. C.	M	60	1,210	1,030	1,260	1,200	.....	1,240	.....	Arteriosclerotic heart disease; hypertension
46	M. R.	M	61	980	1,080	1,110	1,095	.....	1,100	.....	Arteriosclerotic heart disease; hypertension
47	D. G.	M	62	1,150	1,000	1,290	1,100	1,160	1,220	.....	Arteriosclerosis; hypertension
48	A. L.	M	62	1,120	1,120	1,180	1,110	.....	1,220	.....	Arteriosclerotic heart disease
49	E. O.	M	65	1,010	990	.....	1,120	.....	1,130	.....	Angina pectoris
50	J. F.	M	68	1,060	1,040	1,020	870	910	960	.....	Arteriosclerotic heart disease
Maximum				1,580	1,490	1,450	1,460	.....	1,540		
Average				1,030	1,067	1,094	1,082	.....	1,109		
Minimum				730	760	805	810	.....	760		

test in a large series of cases, and found that the blood sugar curves could also be differentiated into the three varieties indicated.

In the group exhibiting the ascending curve, the maximum increase, with but few exceptions, lay between the third and sixth hours and had a definite tendency to occur later rather than earlier in the curve. The largest increase above the fasting level was 640 mg., or 60 per cent. The rise in the total lipid was rarely progressive, as a marked dip in the curve was often present, usually at the fourth hour, sometimes at the third hour and occasionally as early as the second hour. In only a few instances had the total lipid fallen to or below the fasting level at the sixth hour.

The flat type of curve did not usually approximate a straight line, but showed variations of less than 100 mg. either above or below the basal line.

The descending type of curve exhibited either a progressive fall in the total lipid with each determination or, after a steep decline, there was a terminal approach toward the fasting level. The greatest fall from the fasting level was 620 mg.

The fluctuations in the total lipid apparently had no relationship to the variation in the composition or in the conditions under which the test was performed in both groups. When the average total lipid for each determination in the test was plotted (chart 1), two parallel lines were formed. The only difference between them was that the level of the group B curve was 200 mg. higher than that of group A. This difference can be attributed to the inclusion of cases of nephritis in the former, many of which showed an initial lipemia.

Pronounced changes in the curves developed, however, when the entire series was subdivided on the basis of age and on the presence of arteriosclerosis, and the average total lipid was now charted (chart 2). The persons below the age of 35 exhibited a flat curve, the maximum

increase of 60 mg. at the second hour remaining almost stationary to the sixth. Those over 35 years of age showed an ascending curve, which mounted rapidly to the fourth hour and then more slowly to its peak at the sixth hour. The average rise was 167 mg. The patients with moderate or advanced arteriosclerosis were all above 35 years of age, but when they were separately considered, the marked progressive increase

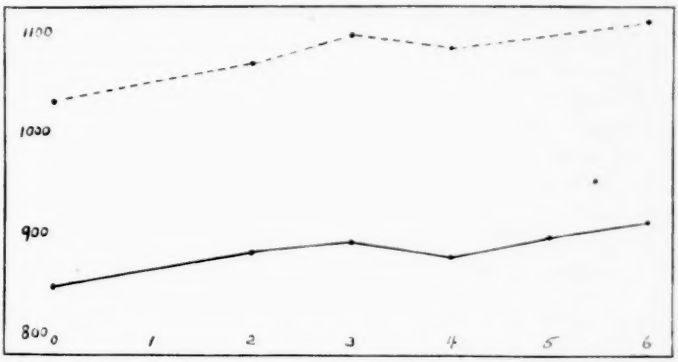

Chart 1.—The average total blood lipid curves of groups A and B. The normal group (A) is represented by the solid line; the ward patients (B), by the dash line. The vertical scale indicates milligrams of total lipid per hundred cubic centimeters of blood; the horizontal scale, hours after the ingestion of olive oil.

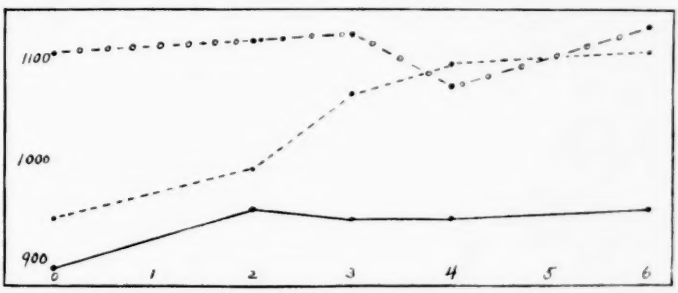

Chart 2.—The average total blood lipid curves of persons below the age of 35 (solid line), of those above the age of 35 (dash line) and of those showing the presence of arteriosclerosis (circle line). The vertical scale indicates milligrams of total lipid per hundred cubic centimeters of blood; the horizontal scale, hours after the ingestion of olive oil.

in the total lipid was completely obliterated. Besides a pronounced drop at the fourth hour, the arteriosclerotic curve was even flatter than that of the younger group, as the maximum increase was but 26 mg. The average fasting level of the total lipid was only slightly influenced by

the age of the subject in contrast to its marked elevation by arteriosclerosis. Summarizing these observations in terms of the three types of curves: Subjects in the second and third decades usually exhibited a flat plateau, those in the fourth, fifth and sixth decades an ascending curve, and those showing evidence of arteriosclerosis a flat or descending curve with a higher fasting level.

Starvation produced a moderate progressive increase in the total blood lipid, the average rise being 75 mg. The substitution of 100 Gm. of dextrose for the olive oil eliminated this starvation effect, and the resultant curve was practically a straight line (tables 3 and 4, chart 3).

Not only is the number of observations on the effect of fat feeding on the blood fat in both normal and pathologic states meager but the kind and amount of fat used and the technic of the blood analyses reported differ so widely that it is difficult to compare them with those in this study.

As early as 1907 Neumann [2] found that ultramicroscopic particles were to be seen in the blood two hours after a meal containing fat and

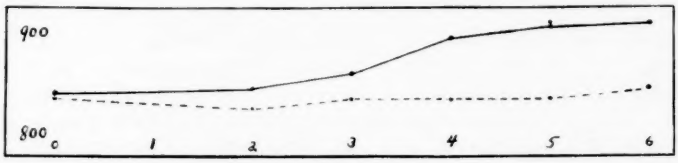

Chart 3.—The average total blood lipid curves in starvation (solid line) and after the ingestion of 100 Gm. of dextrose (dash line). The vertical scale indicates milligrams of lipid per hundred cubic centimeters of blood; the horizontal scale, hours.

that these were not present in the fasting state or after a fat-free meal. Recently, Strauss [3] examined the blood with the dark field for these particles from two to two and a half hours after a meal of 20 Gm. of butter. He reported either no increase or a lowered blood fat in many patients suffering from senility, chronic alcoholism, chronic nephritis, chronic cardiorenal disease and cirrhosis of the liver.

In the same year, Neisser and Braüning [4] found that human serum was almost milky from three to five hours after the ingestion of 100 Gm. of fat. Its turbidity was most marked six hours after the meal, and

2. Neumann, A.: Ueber die Beobachtung des resorbierten Fettes im Blute mittels des Ultra-Condensers, Zentralbl. f. Physiol. **21**:102, 1907.

3. Strauss, H.: Prüfung der Fettresorption durch Erzeugung von alimentärer Lipämie, Klin. Wchnschr. **8**:2047, 1929.

4. Neisser, E., and Braüning, H.: Verdauungslipämie, Ztschr. f. exper. Path. u. Therap. **4**:747, 1907.

it returned to normal six hours later. Bürger and Habs [5] employed this observation, but modified the meal by adding 5 Gm. of cholesterol to 100 cc. of olive oil. They reported a pronounced turbidity of the serum four hours after the meal in all their cases except those of cirrhosis of the liver. Elmer and Scheps,[6] using the same technic, found the test to be wholly unreliable, as in two thirds of their normal cases the serum was either clear or only slightly turbid. Wendt [7] reported the same test negative in other conditions besides cirrhosis of the liver, such as abdominal carcinosis, tuberculous peritonitis, thrombosis of the portal vein, pericardial effusion and amyloidosis. Hirsch [8] added to this list complete occlusion of the common bile duct and a general depression of reabsorption, as in fevers and cachexia.

TABLE 3.—*Variation in the Total Blood Lipid in Starvation*

				Total Lipid, Mg. per 100 Cc.					
Case	Patient	Sex	Age	Fasting	2 Hrs.	3 Hrs.	4 Hrs.	5 Hrs.	6 Hrs.
1	R. O.	M	23	880	890	890	900	920	940
2	S. H.	M	33	800	800	830	890	890	880

TABLE 4.—*Variation in the Total Blood Lipid Following the Ingestion of Dextrose*

				Total Lipid, Mg. per 100 Cc.					
Case	Patient	Sex	Age	Fasting	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	5 Hrs.
1	R. O.	M	23	860	840	840	840	860	880
2	S. H.	M	33	810	810	830	830	810	810

Bloor's nephelometric methods for blood fat have been made use of by several investigators. Cowie and Hoag [9] determined the total lipid content after a meal of analyzed cream in eight normal subjects, five children and three adults. They found it to be increased in all, with its maximum between the fifth and seventh hours in the former and at the sixth hour in the latter. They did not state either the amount or the percentage of increase. Starvation for four days in a boy aged 7 years caused the total lipid to increase 182 per cent, and in another subject,

5. Bürger, M., and Habs, H.: Ueber Störungen der Cholesterin und Fettresorption bei Lebercirrhose, Klin. Wchnschr. **6**:2125, 1927; Die alimentäre hypercholesterinämie beim stoffwechselgesunden Menschen, Ztschr. f. d. ges. exper. Med. **56**:640, 1927.

6. Elmer, A. W., and Scheps, M.: Die Cholesterin-Fettprobe bei Lebercirrhose, Klin. Wchnschr. **7**:1083, 1928.

7. Wendt, H.: Ueber Störungen der Fettresorption bei Lebercirrhose und anderen Erkrankungen, Klin. Wchnschr. **8**:1566, 1929.

8. Hirsch, A.: Ueber alimentäre Lipämie, Klin. Wchnschr. **9**:2062, 1930.

9. Cowie, D. M., and Hoag, L. A.: Studies in Blood Fat, J. A. M. A. **77**: 1493 (Nov. 5) 1921.

64 per cent. Van Slyke and his co-workers [10] fed 1 Gm. of butter per kilogram to six normal subjects and seven patients with nephritis. Of the former, one showed an increase of 80 per cent, four an increase ranging from 1.3 to 29 per cent and one a decrease in the fatty acids of the plasma. Five nephritic patients with an initial lipemia exhibited increases of from 14.5 to 72.4 per cent, with an average of 45 per cent. Of the two subjects with a normal fasting level, the fatty acids remained stationary in one and rose but 4.5 per cent in the other. In the four experiments, on normal as well as on abnormal subjects, in which there was no increase of fat in the plasma, the rise in the metabolic rate and the fall in the respiratory quotient seemed to indicate that, nevertheless, fat was being effectively conveyed to the tissues. McClure and Huntsinger [11] reported an increase in the total fatty acids in fifteen normal subjects after a variety of food-stuffs such as oleic acid, olive oil (50 cc.), dextrose, egg-white and a fat-free meal. This occurred between the third and the fifth hour except with the fat-free meal, when it was present at the third hour. The rise was most pronounced with oleic acid and olive oil. Starvation caused a rise of 12 per cent in one case, but in the others the changes were negligible. Page, Pasternack and Burt,[12] using 100 cc. of olive oil as the meal, found the total lipid increased in seven of eight normal subjects.

Bang,[13] with his own method for estimating the fatty acids of the blood and a mixed meal containing 150 Gm. of fat in the form of butter and cream, reported that most of his cases showed a slight rise, several no increase and one a decrease.

Even a cursory review of the literature indicates that a typical curve has not been obtained with any of the methods employed, and that the cause of these divergent results must be sought in the many uncontrolled factors present in such investigations, including the present one. Fluctuations in the blood fat can be explained in three ways: by variations in the rate of absorption of the ingested fat, in the mobilization of fat from the depots and in the rate of elimination of fat from the blood stream.

The rate of absorption is dependent on a large number of conditions: the emptying time of the stomach, the quantity and quality of the bile, the potency of the steapsin secreted by the pancreas and the state of the intestinal mucosa. Undoubtedly variations in these factors are present

10. Heller, A.; Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: Fat Metabolism in Nephritis, J. Exper. Med. **39**:931, 1924.

11. McClure, C. W., and Huntsinger, M. E.: Studies in Fat Metabolism. J. Biol. Chem. **76**:1, 1928.

12. Page, I. H.; Pasternack, L., and Burt, M. L.: Ueber den Transport von Fetten und Lipoiden durch Blut nach Oleingabe, Biochem. Ztschr. **223**:445, 1930.

13. Bang, I.: Ueber Lipämie, Biochem. Ztschr. **91**:104, 1918.

in apparently normal persons. However, such differences, even to the point of complete lack of absorption, could not explain a decrease in the blood fat. In addition, in the present experiments and in several of the reported cases, starvation produced a rise in the blood lipid.

It is well known that the large stores of fat that the body contains can be put at the disposal of tissues in need of a source of energy. Whether mobilization of the reserve fat occurs in human beings during fat digestion and absorption is still unproved. The discrepancy in the iodine number of the increased blood fat after the drinking of olive oil from that theoretically expected, as observed by McClure and Huntsinger,[11] indicates that such mobilization may take place. Such a phenomenon, however, could only elevate the blood fat.

On the basis of a single variant, only differences in the rate of elimination could explain the three types of curve obtained in this study and by other investigators. Whether the rate of elimination actually varies is unknown. However, it is highly probable that all three factors play a rôle, comparable to the sugar regulatory mechanism, and that the blood fat at any particular time is the resultant of the interplay of these forces. How the age of the subject or the presence of arteriosclerosis modifies these factors is not elucidated by these experiments.

SUMMARY

1. The total blood lipid curves after the ingestion of 100 cc. of olive oil in sixty-seven subjects who were apparently free from pancreatic or hepatic disease are presented.

2. The curves could be subdivided into three categories: ascending, 63.2 per cent; flat, 17.5 per cent, and descending, 19.3 per cent.

3. The age of the subject and the presence of arteriosclerosis markedly influenced the total blood lipid. Persons in the second and third decades presented a flat curve, those in the fourth, fifth and sixth decades an ascending curve and those showing evidence of arteriosclerosis a flat or descending curve.

4. Starvation produced a moderate progressive rise in the total blood lipid.

5. Dextrose eliminated the starvation effect.

INFLUENCE ON CARBOHYDRATE METABOLISM OF EXPERIMENTALLY INDUCED HEPATIC CHANGES

I. FASTING AND ADMINISTRATION OF THYROXINE

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This experimental study was undertaken in an attempt to gain more information on certain disturbances of carbohydrate metabolism previously noted in patients with diseases of the liver.[1] The outstanding abnormality was on insufficiency of the blood sugar-regulating mechanism of the liver revealed by a modification of the dextrose tolerance test. Following the injection of 20 units of insulin and the oral administration of 50 Gm. of dextrose in 1,500 cc. of water, normal persons were found to have a blood sugar curve that differed little from that obtained after the administration of 50 Gm. of dextrose alone. On the other hand, patients with hepatic disease after this test usually showed an initial rise of the blood sugar, which often exceeded the normal, and which was followed by an abrupt decline. In some cases there was no initial rise, but an uninterrupted diminution of the blood sugar level. Both types of curves ended in marked hypoglycemia.

The questions involved in this series of experiments were: (*a*) Can a low glycogen content of the liver, so often present in diseases of this organ, be responsible for deficient regulation of blood sugar? (*b*) Can one or both types of abnormal curves be reproduced in animals under similar conditions following the administration of the so-called specific hepatic poisons—phosphorus and chloroform? The effects of these poisons on carbohydrate metabolism are discussed in papers II and III of this series.

From the Medizinische Universitätsklinik, Leipzig, Prof. Dr. Morawitz, Director.

* Fellow of the J. Simon Guggenheim Memorial Foundation, from the Department of Medicine, University of California Medical School.

1. Althausen, T. L.; Gunther, L.; Lagen, J. B., and Kerr, W. J.: Modification of the Dextrose Tolerance Test as an Index of Metabolic Activity of the Liver, Arch. Int. Med. **46:1** (Sept.) 1930.

The important part played by the glycogen content of the liver in the functional activity of this organ and the diminution of this substance in the livers of many patients with hepatic disorders served as an inducement to investigate the possibility that a reduced amount of hepatic glycogen *per se* might be responsible for hypoglycemia following the modified dextrose tolerance test.

The view that the glycogen is not a storage form of sugar but that it represents a balance between the processes of glycogenesis and glycogenolysis, which in turn are dependent on other phases of utilization of carbohydrates in the body, at present compels its acceptance by weight of experimental evidence. However, this does not preclude the possibility that a low glycogen content of the liver may be connected with abnormalities of sugar metabolism. This concept merely shifts the ultimate responsibility to conditions causing the reduction of hepatic glycogen.

Starvation was employed as one method of reducing the glycogen of the liver. For a check on the obtained results, thyroxine was employed in another series of animals.

METHODS

Young growing rabbits, nearly of the same age and weighing between 1,750 and 2,000 Gm., were selected as the most suitable animals for our purpose. Of these a few grew during the experiments to weigh between 2,000 and 2,200 Gm. Previous to any experiments, the rabbits were kept for at least two weeks on a constant diet of oats, which yield about 60 per cent anions and 40 per cent kations in the ash, and of green vegetables, in the ash of which the proportion of the respective ions is reversed. This was considered important, since Abderhalden and Wertheimer [2] demonstrated that changes of the acid-base balance induced in rabbits by diet affect the potency of insulin and epinephrine in these animals.

It was found that the combination of 5 Gm. of dextrose in 100 cc. of water administered by stomach tube immediately followed by a subcutaneous injection of 1 unit of insulin produced in rabbits a blood sugar curve similar to that of normal persons after the modified dextrose tolerance test. The usual previous overnight fasting was omitted in these animals because the morning blood sugar is lowered by this procedure and because considerable hypoglycemia had been observed between two and three hours after the test in fasting animals. In addition, very little would have been gained by it, since food is normally still found in the digestive tract of rabbits after five days of fasting.

The amount of dextrose chosen for the tolerance test was as small as possible in order to prevent distortion of the blood sugar curves due to glycosuria. The dosage of insulin (0.5 units per kilogram of body weight) and the amount of water were also kept as low as was consistent with a definite physiologic action in order to avoid overwhelming effects and to approach the relative amounts used for patients.

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2. Abderhalden, E., and Wertheimer, E.: Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkrekstoffe: III. Insulin- und Adrenalinwirkung bei Verabreichung "saurer" beziehungweise "basischer" Nährung, Arch. f. d. ges. Physiol. **205**:559, 1929.

In every experiment a specimen of blood sugar was taken from an ear vein before the test. After the administration of dextrose, water and insulin, two samples of blood were obtained at intervals of thirty minutes and two more at intervals of one hour. At the end of three hours the rabbits usually were given subcutaneous injections of 0.1 mg. of epinephrine, and the blood sugar level was followed for two more hours at thirty minute intervals. In the use of this dose of epinephrine the object was to produce a rise in blood sugar that would begin to decline within the period of observation.

Determinations of the blood sugar were made each time in duplicate, according to the method described by Hagedorn and Jensen.[3]

For glycogen analysis of the liver, rabbits were killed by decapitation or by a blow below the occiput. From 10 to 20 Gm. of hepatic tissue, amounting to from

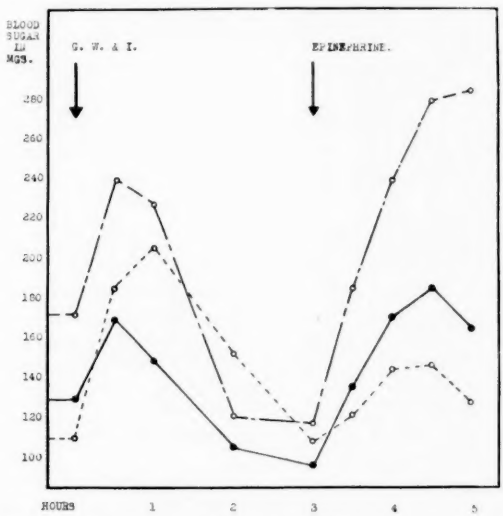

Chart 1.—Blood sugar curves after the modified dextrose tolerance test and the administration of epinephrine in normal rabbits, fasting rabbits and those treated with thyroxine. The solid line represents an average of thirty-seven tests on normal rabbits. The regularly broken line shows the average of four tests on fasting rabbits. The irregularly broken line traces the curve of rabbit 751, which received the largest amount of thyroxine.

30 to 50 per cent of the total weight of the liver, was ground in ice-cooled alcohol and used for determinations of the glycogen by the Pflüger-Bertrand method. The glycogen determinations were made by Dr. Thoenes.

For histologic examination of the liver, two deep wedge-shaped pieces of tissue were removed from different parts of this organ and fixed in a diluted solution of formaldehyde, U. S. P. (1:10). From one part of the specimen, 5 micron paraffin sections were stained with hematoxylin and eosin. Frozen sections from the other part were stained with sudan III.

3. Hagedorn, H. C., and Jensen, N.: Zur Mikrobestimmung des Blutzuckers mittels, Ferricyanid, Biochem. Ztschr. **135**:46, 1923; ibid. **137**:92, 1923.

TABLE 1.—*Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Normal Rabbits*

Number	Weight, Gm.	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose, Water and Insulin	Difference Between Average Blood Sugar for 3 Hr. and Initial Blood Sugar	Average Blood Sugar for 2 Hr. After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr. Blood Sugar
		Initial Blood Sugar	½ Hr.	1 Hr.	2 Hr.	3 Hr.	3½ Hr.	4 Hr.	4½ Hr.	5 Hr.				
717a*	2,030	112	155	162	119	83	112	151	194	166	129	+17	145	+ 62
717b*	2,030	111	140	144	119	94	151	205	209	230	124	+13	182	+ 88
718	2,170	126	202	176	148	115	216	205	256	248	157	+31	215	+100
734a	1,800	124	130	140	104	83	158	151	144	140	116	+ 8	141	+ 58
734b	1,800	151	205	169	83	90	115	162	187	162	124	+14	148	+ 58
735a	1,950	140	184	166	112	133	122	148	140	162	147	+ 8	140	+ 7
735b	1,950	137	176	151	137	144	...	...	...	...	148	+11	...	.....
738	1,950	151	181	126	133	115	151	151	194	144	138	−13	157	+ 42
739	1,750	126	155	122	112	115	166	144	144	137	123	− 3	145	+ 30
740a	1,750	126	202	187	112	90	119	187	187	155	158	+32	154	+ 64
740b	1,750	130	155	119	83	104	133	184	151	133	112	−18	144	+ 40
741	1,900	162	191	169	126	119	140	216	205	158	150	−12	178	+ 59
749	2,170	137	209	158	90	94	119	209	209	184	132	− 5	164	+ 70
751	2,040	122	140	101	86	101	115	187	227	187	104	−18	224	+123
760	2,130	115	148	108	86	94	140	220	225	209	106	− 9	193	+ 99
801a	1,850	133	169	162	148	151	173	144	158	148	154	+21	148	+ 12
801b*	1,850	151	176	156	148	137	140	166	166	151	153	+ 2	163	+ 11
803	1,770	133	155	126	108	119	140	158	151	151	124	− 9	146	+ 27
804	1,770	158	162	104	104	72	119	154	158	144	126	−32	135	+ 63
811a	1,800	169	205	176	93	72	101	131	152	131	135	−34	121	+ 49
811b	1,800	141	227	184	126	61	...	...	...	...	148	+ 7	...	.....
814	1,700	108	130	137	108	65	...	...	...	...	112	+ 4	...	.....
816†	1,860	119	133	126	90	97	...	119	...	133	110	− 9	...	.....
818	1,950	122	155	148	122	79	...	...	...	...	127	+ 5	...	.....
821	2,000	97	151	119	76	79	...	...	...	...	102	+ 5	...	.....
823	1,850	130	166	140	94	94	...	...	...	...	121	− 9	...	.....
824	1,850	151	187	158	115	104	...	...	...	...	139	−12	...	.....
826	1,750	126	144	133	97	83	...	...	...	...	114	−12	...	.....
828†	1,880	144	176	173	108	115	112	126	122	115	140	− 4	...	.....
829	1,760	137	212	202	108	119	...	...	...	...	153	+16	...	.....
830	2,160	151	194	173	137	130	...	...	...	...	156	+ 5	...	.....
831	1,850	115	169	137	83	90	...	...	...	...	115	0	...	.....
832	2,020	158	180	168	108	90	...	...	...	...	137	−20	...	.....
833	1,920	122	162	122	58	79	...	...	...	...	101	−21	...	.....
834	1,950	144	169	144	101	108	...	...	...	...	128	−16	...	.....
835	1,780	108	155	155	104	58	...	...	...	...	118	+10	...	.....
836	1,720	112	133	94	83	97	...	...	...	...	99	−13	...	.....
Average	.....	132	170	150	107	99	137	173	186	167	129	− 3	157	+58

RESULTS

Normal Rabbits.—Blood sugar curves three hours following the administration of dextrose, water and insulin were made on thirty-seven occasions for thirty-one normal rabbits. The individual data are given in table 1, and the average curve is plotted in chart 1. From the presented data it is seen that a normal curve, under the conditions of the test, has a characteristic shape and, within limits, a certain height.

As a basis of quantitative comparison with abnormal curves, the average blood sugar during the three hours of the test and the algebraic difference between the initial blood sugar and this average were found very useful. The peak of the curves usually paralleled the average blood sugar, but on the whole was less reliable. In two rabbits (816 and 828)

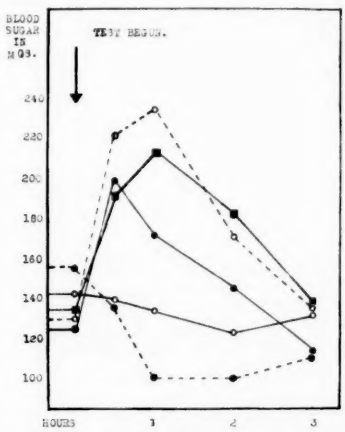

Chart 2.—Blood sugar curves of a normal rabbit (718) after the administration of various combinations of dextrose, water and insulin. The solid line with disks shows the curve after the administration of dextrose, water and insulin; the solid line with squares, that after dextrose and water; the broken line with circles, after dextrose alone; the solid line with circles, after water only, and the broken line with disks after insulin alone.

that were followed for five hours after the test there was a gradual rise of the curve following a minimum at two hours.

In order to appraise the significance of the various factors involved in the production of the "normal" three hour curve, a series of experiments was carried out in which dextrose, water and insulin were given to the same rabbit singly and in various combinations, followed by the usual observations on the blood sugar. The results are given in table 2 and chart 2. Data on normal epinephrine curves are shown in table 1 and chart 1. From this the peak of the hyperglycemia due to epi-

TABLE 2.—*Blood Sugar Curves After the Administration of Various Combinations of Dextrose, Water and Insulin in Two Normal Rabbits*

No.	Test	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose, Water and Insulin	Difference Between Average Blood Sugar for 3 Hr. and Initial Blood Sugar	Average Blood Sugar for 2 Hr. After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr. Blood Sugar
		Initial Blood Sugar	½ Hr.	1 Hr.	2 Hr.	3 Hr.	3½ Hr.	4 Hr.	4½ Hr.	5 Hr.				
718	Dextrose, water and insulin	126	202	176	148	115	216	205	256	248	157	+31	215	+100
718	Dextrose and water.....	137	194	216	187	140	184	234	230	209	183	+46	232	+ 92
718	Dextrose.....	133	223	238	173	137	...	...	...	...	189	+56	...	.....
718	Dextrose.....	176	245	255	259	155	...	...	...	...	232	+56	...	.....
718	Water.....	144	140	137	126	137	205	223	263	...	134	−10	209	+ 72
718	Insulin.....	158	140	101	101	115	173	223	205	162	115	−43	185	+ 70
826	Dextrose, water and insulin	126	144	133	97	83	...	...	...	...	114	−12	...	.....
826	Dextrose.....	152	209	173	144	144	...	...	...	...	163	+11	...	.....

TABLE 3.—*Glycogen Content of the Liver Before and After the Modified Dextrose Tolerance Test*

Normal Rabbits				Fasting Rabbits				Thyroxine Treated Rabbits			
Before Dextrose, Water and Insulin		After Dextrose, Water and Insulin		Before Dextrose, Water and Insulin		After Dextrose, Water and Insulin		Before Dextrose, Water and Insulin		After Dextrose, Water and Insulin	
Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent
23	5.70	807	10.8	20	0.7	810	2.25	742	0.6	802	2.20
176	4.50	808	9.6	775	1.0	812	1.55	840	0.7	809	3.04
744	7.85	814	5.2	806	0.6	822	2.17				
827	5.20					838	3.36				
Animals	Average %	Animals	Average %	Animals	Average %	Animals	Average %	Animals	Average %	Animals	Average %
4	5.81	3	8.5	3	0.76	4	2.33	2	0.65	2	2.62

nephrine can be expected to be reached between one and one and a half hours after the injection.

The maximum rise in blood sugar after the administration of epinephrine and especially the average blood sugar for two hours following the injection, as well as the algebraic difference between these values and the blood sugar level before the injection, were of much greater assistance in detecting abnormal responses to epinephrine than the shape of the curve.

Data on the amount of glycogen found in the liver of normal rabbits before and after the modified dextrose tolerance test are given in table 3. From these results it appears that the average glycogen content of the liver was increased by the administration of dextrose, water and insulin from 5.8 Gm. per hundred grams to 8.5. Since these determinations of necessity were made for different animals, and since the higher figure is still within the limits of normal, the possibility must be considered that the increase is only apparent. On the other hand, taking into account the individual data that make up the average figure and the uniformity of the animal material kept on a constant diet, such a possibility does not seem probable.

Fasting Animals.—Rabbits were prepared for the starvation experiment by withdrawal of all food for three days prior to the sugar tolerance and epinephrine tests. Data on the blood sugar curves of four animals subjected to such a fast will be found in table 4. The average curve is plotted in chart 1.

A comparison of blood sugar data obtained after fasting with those of the same animals in the normal state or with the average figures of all normal rabbits reveals several significant abnormalities. In analyzing the shape of the curves it is seen that in fasting rabbits the initial blood sugar is considerably lower. The peaks of the curves are higher than normal and are characteristically placed at the one hour period instead of the half hour period. The two hour blood sugar, which is normally lower than the initial blood sugar, is higher in all four fasting animals. Finally, in three cases even the three hour blood sugar is higher than the initial one. The exception in one case (734) in which the peak reached an unusual height of 230 mg. is probably explained by spilling of sugar into the urine.

Figures for the average blood sugar before fasting, namely, 140 mg. with an increase of 3 mg. for the three hours, and after fasting, 163 mg. with an increase of 51 mg., justify the impression already gained from the shape of the curves that the sugar tolerance of rabbits in this experiment was reduced.

The response to the administration of epinephrine was tested in three fasting animals, and was found markedly reduced in two cases and

TABLE 4.—*Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Fasting Rabbits*

Number	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose, Water and Insulin	Difference Between Average Blood Sugar for 3 Hr. and Initial Blood Sugar	Average Blood Sugar for 2 Hr. After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr. Blood Sugar
	Initial Blood Sugar	½ Hr.	1 Hr.	2 Hr.	3 Hr.	3½ Hr.	4 Hr.	4½ Hr.	5 Hr.				
734	137	191	230	137	86	144	180	173	130	161	+24	151	+65
735	104	198	207	176	112	79	79	94	83	171	+67	88	−24
741	119	173	187	155	148	144	180	180	176	162	+43	167	+19
838	86	180	205	155	94	...	Animal killed		...	156	+70	...	....
Average*	112	186	207	156	110	122	146	149	130	163 (140)	+51 (+3)	135 (155)	+25 (+41)

* In parentheses are given the normal averages for these animals.

TABLE 5.—*Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Rabbits Treated with Thyroxine*

Number	Total Dose of Thyroxine in Mg. per Kg.	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose, Water and Insulin	Difference Between Average Blood Sugar for 3 Hr. and Initial Blood Sugar	Average Blood Sugar for 2 Hr. After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr. Blood Sugar
		Initial Blood Sugar	½ Hr.	1 Hr.	2 Hr.	3 Hr.	3½ Hr.	4 Hr.	4½ Hr.	5 Hr.				
740	5.5	119	144	115	97	151	148	176	184	180	120	+ 1	169	+ 18
739	6.6	124	151	126	86	144	176	216	220	234	120	− 4	225	+ 81
751	7.7	173	241	230	122	119	187	241	281	284	173	0	225	+107

almost unchanged in one. The average blood sugar after the administration of epinephrine for three rabbits before fasting was 155 mg., with an increase of 41 mg. over the three hour blood sugar, while after starvation it was 135 mg., with an increase of only 20 mg. The peaks of the postepinephrine curves in two cases were also correspondingly lower.

As was expected, the hepatic glycogen of the fasting rabbits (table 3) was low, averaging only 0.76 Gm. per hundred grams. After the administration of dextrose, water and insulin similarly to the controls, the glycogen content rose to 2.58 Gm. per hundred cubic centimeters.

Microscopic examination of the liver of two rabbits killed after three days of fasting revealed some shrinking of the trabecula with widening of the spaces between. These changes were more marked near the central veins.

Animals Treated with Thyroxine.—Three rabbits received subcutaneously over a period of five days in equal doses 5.5 mg., 6.6 mg. and 7.7 mg. of thyroxine per kilogram of body weight. In spite of an unlimited amount of the usual food in the cages and an apparently excellent appetite, the animals lost during this time between 11 and 15 per cent of their weight. Aside from moderate emaciation, a certain "jumpiness" was the only observed clinical sign.

The data on the blood sugar obtained from these rabbits are given in table 5, while chart 1 shows the curve for the animal that received the largest dose of thyroxine (751). The sugar tolerance of two rabbits that received the smaller doses of thyroxine was found to be practically unchanged. The only remarkable feature of both curves is the abrupt rise of blood sugar between the second and third hours, representing an accentuation of the return to the normal level, which in these cases is as high as the peak of the respective curves. In the third rabbit, the initial blood sugar and the curve during the first hour of the experiment not only exceed the normal values for this animal, but are higher than those for any normal animal in our series. The average blood sugar during the three hours and the increase over the initial blood sugar are also correspondingly higher. On the other hand, the exaggerated return of the blood sugar to the normal level is lacking.

As to the response to epinephrine of the rabbits treated with thyroxine, even within the two hours of observation the average blood sugar was 206 mg., with an increase of 85 mg. over the three hour blood sugar, versus 173 mg., with an increase of 68 mg. in the same animals when normal. In addition, only the first rabbit showed a small decline in the curve before the end of two hours, while in the other two animals the blood sugar was still on the increase at the end of the experiment. The rabbit treated with the largest doses of thyroxine

exhibited signs of distress following the injection of epinephrine and died during the night.

The average glycogen content of the liver in rabbits treated with thyroxine was 0.65 Gm. per hundred grams. After the modified dextrose tolerance test, it rose to 2.62 Gm. per hundred cubic centimeters (table 3).

Microscopic examination of the livers of two rabbits treated with thyroxine revealed no organic lesions other than shrinkage of the columns of hepatic cells, which was more marked than in those of the fasting animals, and numerous fine brown granules within the cells of the parenchyma.

COMMENT

After the administration of dextrose, water and insulin, fasting rabbits showed a diminished sugar tolerance and following injections of epinephrine a less marked rise in blood sugar. Reduction of the sugar tolerance through fasting was discovered by Bang,[4] who attributed it to a reduced ability on the part of the liver to form glycogen. According to Staub,[5] fasting leads to inhibition of the formation of insulin and thus retards the utilization of sugar. Finally, Elias [6] advanced the theory that acidosis due to hunger is responsible for the diminished sugar tolerance through slower formation of glycogen and retardation of absorption of sugar by the tissues. Van Noorden and Isaac [7] modernized the theory of Bang by the supposition that the formation of glycogen in the liver is dependent on the existing supply of glycogen in this organ from which energy for the polymerization of dextrose is derived through its transformation into lactic acid. In addition, they concede the possibility of a temporary insufficiency of insulin as a contributing factor.

In the present experiment, the glycogen content of the normal liver after the administration of dextrose, water and insulin was found to be about 50 per cent higher than that of the controls. In the fasting group, the amount of hepatic glycogen after the modified dextrose tolerance test was three times as great as that in the fasting controls. The absolute increase in glycogen amounted to 2.7 Gm. per hundred grams of hepatic tissue in the normal rabbits and to only 1.6 Gm. in the fasting animals. Since the possible insufficiency of insulin in this experiment was counteracted by exogenous insulin, it appears that

4. Bang, J.: Der Blutzucker, Wiesbaden, J. F. Bergmann, 1913.

5. Staub, H.: Untersuchungen über den Zuckerstoffwechsel des Menschen, Ztschr. f. klin. Med. **91**:44, 1921; ibid. **93**:89, 1922.

6. Elias, H.: Zur Bedeutung des Säurebasenaushaltes und seiner Störungen, Ergebn. d. inn. Med. u. Kinderh. **25**:192, 1924.

7. von Noorden, G., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, Berlin, Julius Springer, 1927, p. 33.

diminution of the existing supply of hepatic glycogen in fasting animals is at least in part responsible for the slower deposition of glycogen in the liver, which in its turn makes for a reduced sugar tolerance.

Diminution of the response to epinephrine in the fasting rabbits was in all probability caused by a low glycogen content of the liver. It is true that recent experiments by Cori and Cori [8] tend to show that other factors such as reduced utilization of blood sugar by the tissues, may enter into the production of hyperglycemia after the administration of epinephrine, yet the work of Sahyun and Luck [9] demonstrated anew that mobilization of hepatic glycogen is an important part of the action of this hormone, at least during the first two hours after the injection.

Deviations from the normal of blood sugar curves observed in three rabbits treated with thyroxine are in accord with the work of Burn and Marks,[10] and of Marks.[11] The exaggerated return of the blood sugar to normal in the first two animals is due to the fact that thyroxine renders the liver overresponsive to stimuli that promote a discharge of sugar into the blood. In this case such a stimulus was provided by lowering of the blood sugar. On the other hand, this overactivity of the liver can find expression only in the presence of a certain minimum of glycogen in this organ. Therefore this phenomenon is absent in the case of the third rabbit, which received the largest dose of thyroxine.

The normally shaped but very high three hour blood sugar curve of the same animal is caused by a decrease of the hypoglycemic reaction to insulin typically produced by the administration of thyroid extract over a certain length of time. Finally, the increased hyperglycemia after the administration of epinephrine is explained by sensitization of the liver to this hormone as already observed by the authors mentioned. It is of interest that the increased reaction to epinephrine in our experiment was produced by smaller doses of thyroxine than were necessary to bring about a decrease in the response to insulin.

The average glycogen content of the liver of rabbits treated with thyroxine was slightly below that of the fasting animals, and the hepatic glycogen after the administration of dextrose, water and insulin showed approximately the same increase. This similarity in regard to the

8. Cori, C. F., and Cori, G. T.: The Mechanism of Epinephrine Action; Influence of Epinephrine on Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, J. Biol. Chem. **79**:309 (Sept.) 1928; Mechanism of Epinephrine Action; Influence of Epinephrine and Insulin on Carbohydrate Metabolism of Rats in Postabsorptive State, ibid. **79**:321.

9. Sahyun, M., and Luck, J. M.: The Influence of Epinephrine and Insulin on the Distribution of Glycogen in Rabbits, J. Biol. Chem. **85**:1, 1929.

10. Burn, J. H., and Marks, H. P.: The Relation of the Thyroid Gland to the Action of Insulin, J. Physiol. **60**:131, 1925.

11. Marks, H. P.: Effect of Thyroid Feeding on Sugar Tolerance, J. Physiol. **60**:402, 1925.

accumulation of glycogen in two sets of animals in which reduction of hepatic glycogen was accomplished in such different ways is of considerable interest in view of the very dissimilar blood sugar curves obtained for the two groups.

Neither in rabbits in which the glycogen of the liver was reduced by fasting, nor in animals in which the same object was accomplished with injections of thyroxine did the blood sugar curves show the characteristic hypoglycemia observed in persons suffering from diseases of the liver. From this it seems improbable that the described disturbance of the carbohydrate-regulating mechanism in man is caused by lowering of hepatic glycogen. We find clinical confirmation of this conclusion in the observation that patients with diabetes, a disease in which the glycogen of the liver is always reduced, do not show hypoglycemia curves after the modified dextrose tolerance test except when other evidence of hepatic insufficiency is present.

SUMMARY

Normal, fasting rabbits treated with thyroxine were subjected to a modification of the dextrose tolerance test followed by an injection of epinephrine. Blood sugar curves following these procedures and determinations of the hepatic glycogen before and after the modified dextrose tolerance test were made.

The fasting animals were found to have reduced tolerance to sugar and diminished response to epinephrine, both apparently due to a lowered glycogen content of the liver. The rabbits treated with thyroxine showed increased susceptibility to glycogenolytic stimuli and a decrease of hepatic glycogen.

In neither of these two groups did the lowering of the glycogen content of the liver produce the hypoglycemia so typical in patients with hepatic diseases after the modified dextrose tolerance test.

All rabbits showed an increase in the hepatic glycogen after the administration of dextrose, water and insulin.

INFLUENCE ON CARBOHYDRATE METABOLISM OF EXPERIMENTALLY INDUCED HEPATIC CHANGES

II. PHOSPHORUS POISONING

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In order to produce a diffuse injury of the hepatic parenchyma with as little damage as possible to other organs, the two classic poisons phosphorus and chloroform were used. Anatomically, phosphorus, according to Mosiman and Whipple,[1] attacks chiefly the cell protoplasm. The lesions produced by moderate phosphorus poisoning consist of fatty degeneration, which is described by Opie and Alford [2] as usually appearing in the early stages in the center of the lobules, while later it is most conspicuous near the portal spaces. Severe poisoning by phosphorus produces coagulative necrosis, which has a tendency to be at the periphery of the lobules.

Phosphorus may produce fatty degeneration of a moderate degree also in other organs. However, to quote from an article on the hepatic factor in chloroform and phosphorus poisoning by Williamson and Mann,[3] "The liver is the most seriously damaged organ histologically and physiologically." Opie and Alford, on the basis of their work, came to similar conclusions.

CHRONIC PHOSPHORUS POISONING

Phosphorus was given in all our experiments by subcutaneous injections in the form of 0.5 per cent solution in oil. In some preliminary

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1. Mosiman, R. E., and Whipple, G. H.: Chloroform Poisoning, Bull. Johns Hopkins Hosp. **23**:323 (Nov.) 1912.

2. Opie, E. L., and Alford, L. B.: Diet and the Hepatic Lesions of Chloroform, Phosphorus, or Alcohol, J. Exper. Med. **21**:1, 1915.

3. Williamson, C. S., and Mann, F. C.: Studies on Physiology of Liver: The Hepatic Factor in Chloroform and Phosphorus Poisoning, Am. J. Physiol. **65**:267, 1923.

experiments, daily doses of 1 mg. of phosphorus per kilogram of body weight resulted in the death of the animal within five days. The dose was then reduced to 0.85 mg. and produced a fatal outcome in nine days. Finally, 0.75 mg. of phosphorus per kilogram was chosen as the daily dose, and was employed in eight rabbits. Of these animals two died after twelve injections, one succumbed to thirteen doses, and one survived fifteen injections. Two rabbits were killed after ten injections, and two were used for recovery experiments with temporary withdrawal of phosphorus following nine and ten injections, respectively.

On these chronically poisoned rabbits blood sugar curves were made following the administration of dextrose, water and insulin, and also after epinephrine, beginning with the fifth day.[4] The results of the numerous experiments are reported in separate protocols for each animal (table 1), and in addition, the average figures for the various stages are shown in table 2. Figures for the glycogen content of the livers of these animals before and after the modified dextrose tolerance test are given in table 3.

Results.—Four Day Stage: In two rabbits examined four days after the beginning of the injections of phosphorus, the initial blood sugar was found to be lowered. The peak of the curves was at the normal period, but the two hour blood sugar was high. The average blood sugar was somewhat lower than that of the same animals when normal, but the increase over the initial level was marked. The epinephrine response in these rabbits was almost two times greater than normal, whether judged by the average blood sugar or by the peak of the curve. The hepatic glycogen in two rabbits was reduced to 0.6 per cent.

Six Day Stage: In three animals tested on this day the findings were essentially similar to those found at the preceding stage. The hyperglycemia after epinephrine was greater than normal in two rabbits and lower in one. The highest blood sugar in all three curves following epinephrine was observed in the last specimen.

Eight Day Stage: In two animals at this phase of the action of phosphorus, in addition to a low initial blood sugar and a lower average blood sugar with a greater increase over the initial level, the peak of the curve after the administration of dextrose, water and insulin was found at the one hour period. Likewise the epinephrine response was below normal, coincident with a drop of the curve during the first half hour after the injection. The maximum blood sugar after the use of this hormone was again reached at the end of two hours.

4. For description of methods see our first paper: The Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: I. Fasting and Thyroxine Administration, Arch. Ind. Med., this issue, p. 46.

TABLE 1.—*Blood Sugar Curves After the Modified Dextrose Tolerane Test and the Administration of Epinephrine in Rabbits Subjected to Chronic Phosphorus Poisoning*

Number	Number of Days Since Beginning of Poisoning	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose Water and Insulin	Difference Between Average Blood Sugar for 3 Hr. and Initial Blood Sugar	Average Blood Sugar for 2 Hr. After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr.
		Initial Blood Sugar	½ Hr.	1 Hr.	2 Hr.	3 Hr.	3½ Hr.	4 Hr.	4½ Hr.	5 Hr.				
735	Normal	138	180	158	125	139	122	148	140	162	148	+10	140	+ 7
	4	126	198	184	151	126	151	187	202	191	161	+45	175	+49
	6	119	148	133	83	90	126	162	173	173	111	− 8	148	+58
	8	104	140	162	94	104	101	119	137	140	118	+14	120	+16
	Phosphorus continued; rabbit died 6 days later; liver examined													
740	Normal	128	179	153	98	97	126	186	169	144	135	+ 7	149	+52
	10	101	151	144	151	86	76	86	86	97	134	+33	85	− 1
	Phosphorus continued; animal moribund, killed for liver specimen													
741	Normal	162	191	169	126	119	140	216	205	158	150	−12	178	+59
	4	97	158	101	97	79	104	155	191	184	105	+ 8	146	+67
	6	122	162	155	137	119	126	176	169	198	142	+20	158	+39
	8	94	137	162	115	83	68	83	122	144	124	+30	97	+14
	10	122	151	151	115	72	101	104	122	126	124	+ 2	107	+35
	12	72	112	166	176	166	162	187	184	169	153	+81	175	+ 9
	15	108	148	162	133	104	59	59	68	56	136	+28	67	−37
	Phosphorus administration discontinued													
	17	104	148	148	130	115	94	98	86	112	133	+29	98	− 7
	Rabbit died 7 days later; liver examined													
816	Normal*	119	133	126	90	97	...	119	...	133	110	− 9	...	....
	6	119	140	137	148	144	148	180	230	270	141	+22	191	+47
	10	...	...	...	...	54	86	108	130	133	...	....	105	+51
	13	122	112	151	148	133	173	191	187	184	138	+16	178	+45
	Injections of phosphorus continued; rabbit died 2 days later; liver examined													
826	Normal	126	144	133	97	83	...	...	...	...	114	−12	...	....
	9	104	158	158	187	169	176	176	187	185	165	+61	179	+10
	10	94	148	176	176	126	97	119	115	115	157	+63	113	−13
	The following day animal was killed for glycogen analysis of the liver													
828	Normal*	144	176	173	108	115	112	126	122	115	140	− 4	...	....
	10	79	137	144	194	122	90	101	119	112	151	+72	106	−16
	Animal killed next day for glycogen analysis 3 hours after administration of dextrose, water and insulin; liver examined													

881	Normal	115	169	137	83	90	...	...	...	...	115	0	...	....
	9	101	173	184	112	122	112	101	104	97	141	+40	107	—15
	Phosphorus omitted for 1 day													
	10 Injection of phosphorus given	...	..	86	104	112	126	122	...	....	112	+26		
	11	50	79	115	79	79	47	65	47	43	86	+36	55	—24
	12	76	119	148	79	104	76	83	61	68	107	+31	77	—27
	Phosphorus omitted for 2 days													
	13 Administration of phosphorus started													
		104	108	86	101	108	115	126	148	140	100	— 4	138	+30
	14	...	...	...	...	86	94	108	144	136	...	....	114	+28
	16†	101	137	141	137	122	141	202	137	118	133	+32	150	+28
	18†	112	126	140	151	158	119	151	151	191	142	+30	128	—30
	20	76	...	...	...	97	94	108	108	137	...	....	107	+10
	24	...	...	...	...	112	137	180	184	176	...	....	161	+39
	26	...	...	...	...	104	64	113	108	111	...	....	98	— 6
	Animal killed the following day for glycogen analysis 3 hours after administration of dextrose, water and insulin													
883	Normal	122	162	122	58	79	...	...	...	...	101	—21	...	....
	Normal†	122	115	119	104	119	...	...	...	...	114	— 8	...	....
	10	68	119	148	104	76	58	76	61	68	110	+42	67	— 9
	11†	97	115	108	97	119	79	86	97	90	107	+10	92	—27
	Phosphorus omitted for 2 days													
	Injections of phosphorus started again													
	12	104	130	115	94	58	68	68	61	108	100	— 4	70	+12
	13	...	...	...	...	90	90	119	122	126	...	....	110	+20
	15	...	...	...	...	54	68	83	101	115	...	....	84	+30
	17	...	...	...	...	86	119	137	137	130	...	....	125	+39
	18	...	...	...	...	83	83	83	122	122	...	....	98	+15
	21	54	54	65	65	58	40	58	29	18	61	+ 7	41	—17
	Animal died 1 hour after last specimen of blood was taken													

* Five hour curve without epinephrine having been given.

† Sodium lactate only administered.

TABLE 2.—*Significant Average Blood Sugar Figures After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in the Group with Chronic Phosphorus Poisoning* *

Days After Poisoning	Number of Rabbits	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin						Blood Sugar After 0.1 Mg. of Epinephrine			
		Initial Blood Sugar	Peak of Curve	Difference Between Initial Blood Sugar and Peak	Average Blood Sugar for 3 Hr.	Difference Between Average and Initial Blood Sugar	3 Hr. Blood Sugar	Peak of Curve	Difference Between Peak and 3 Hr. Blood Sugar	Average Blood Sugar After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr.
4	2	112	178	+66	133	+21	103	197	+94	161	+58
		(151)	(186)	(+35)	(149)	(— 2)	(126)	(189)	(+57)	(159)	(+33)
6	3‡	120	153	+33	131	+11	118	214	+96	116	+48
		(137)	(168)	(+31)	(136)	(— 1)	(116)				
6	2	...	...	....	...	....	105	186	+81	153	+48
							(126)	(189)	(+57)	(159)	(+33)
8	2	99	162	+63	121	+22	94	142	+49	109	+15
		(151)	(186)	(+35)	(149)	(— 2)	(126)	(189)	(+57)	(159)	(+33)
9	2	103	186	+83	153	+50	146	150	+ 4	143	— 3
		(127)	(157)	(+30)	(115)	(—12)	(87)				
10	6†	93	164	+71	135	+42	89	112	+23	98	+ 9
		(136)	(170)	(+34)	(128)	(— 8)	(98)				
10	2‡	...	...	....	...	....	79	112	+33	96	+17
							(108)	(201)	(+93)	(146)	(+56)
No epinephrine response	6	92	168	77	138	+46	106	99	— 7	91	—15
		(133)	(170)	(+37)	(126)	(—7)	(97)				
No epinephrine response	2‡	...	...	....	...	....	95	83	—12	76	—19
							(108)	(201)	(+93)	(164)	(+56)

* Parentheses indicate the normal average figures for the rabbits.

† Blood specimens corresponding to the first three hours of one curve were not obtained.

‡ Animals for which post-epinephrine curve had been made before poisoning.

Nine Day Stage: Two rabbits examined on this day exhibited to an increased degree all the abnormalities of the three hour curve previously mentioned, and the average blood sugar became higher than that in the normal animals. Furthermore, the maximum elevation of blood sugar was observed in one rabbit at the two hour period. The effect of epinephrine in one case was slight, while in the other a steady falling off of the curve was observed. The average blood sugar in the second rabbit following administration of epinephrine was 15 mg. lower than at the time of injection.

Ten Day Stage: Six animals were tested at this stage. Blood sugar curves of the modified dextrose tolerance test were essentially similar to those of the previous day, only now the peak of the curves was

TABLE 3.—*Glycogen Content of the Liver in Rabbits Poisoned with Phosphorus Before and After the Modified Dextrose Tolerance Test*

Chronic Phosphorus Poisoning 4 Days		Chronic Phosphorus Poisoning, No Response to Epinephrine				Acute Phosphorus Poisoning 14 Hour Stage			
Before Administration of Dextrose, Water and Insulin		Before Administration of Dextrose, Water and Insulin		After Administration of Dextrose, Water and Insulin		Before Administration of Dextrose, Water and Insulin		After Administration of Dextrose, Water and Insulin	
Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent
748	0.5	0	0.3	828	0.5	839	4.01	817	3.42
774	0.7	826	1.9	831	0.3			819	1.30
		904	0.9						
Animals	Average, per Cent	Animals	Average, per Cent	Animals	Average, per Cent	Animals	Average, per Cent	Animals	Average, per Cent
2	0.6	3	1.0	2	0.4	1	4.01	2	2.36

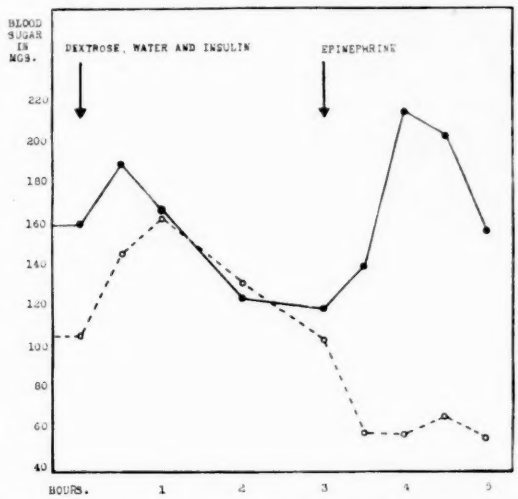
observed at the two hour period in three rabbits. Hypoglycemic curves after the administration of epinephrine were encountered in four cases, and both reduced and delayed responses were found in two cases.

Later Stages: One of the last two rabbits (741) that had the greatest resistance to phosphorus showed a still further reduced response to epinephrine on the thirteenth day and a deep hypoglycemic curve after the administration of this hormone when tested on the sixteenth day of progressive poisoning. Animal 816 had no hypoglycemia after the administration of epinephrine at the thirteen day stage, and was found dead on the morning of the sixteenth day. Finally, a third rabbit (735) had a low epinephrine curve at the eight day stage, and died on the fifteenth day without having been tested again.

Average blood sugar figures for six rabbits that had lost their response to epinephrine are given for convenience at the end of table 2, and a typical blood sugar curve is reproduced in the accompanying

chart. All eleven curves at the stage under discussion are characterized by lowering of the blood sugar half an hour following the injection of epinephrine.

After reaching the stage of phosphorus poisoning in which post-epinephrine hyperglycemia is lacking, the rabbits were either killed for analysis of the liver or were used for special experiments. On one of the latter animals (833), which was used for a recovery experiment and later again given phosphorus, it was possible to make a complete curve one hour before death. The blood sugar level in this rabbit during the first three hours was very low, but the average blood sugar was still higher than the initial value in contrast to the normal curve



A typical blood sugar curve of a rabbit (741) after the modified dextrose tolerance test and the administration of epinephrine. A late stage of chronic phosphorus poisoning is shown by the broken line; the solid line traces the curve obtained previous to poisoning.

of the same animal. The curve after the administration of epinephrine was of the usual hypoglycemic type.

The glycogen content of the livers of three rabbits that lost their response to epinephrine varied between 0.3 per cent and 1.9 per cent, averaging 1 per cent. After the administration of dextrose, water and insulin, the hepatic glycogen in two such animals amounted to only 0.4 per cent.

Special Experiments.—1. Five Hour Sugar Tolerance Curves Without Epinephrine: In order to ascertain whether the hypoglycemia after

the administration of epinephrine was actually caused by this hormone or took place in spite of it, five hour blood sugar curves following the administration of dextrose, water and insulin were obtained in two rabbits in which the epinephrine response was no longer present. In one of these animals (831) the typical hypoglycemic curve was obtained. The other rabbit (833), in which injections of phosphorus had been discontinued two days before, also had a very low curve, but beginning recovery was manifested by a rise of the blood sugar in the last specimen.

2. Utilization of Lactic Acid in Phosphorus Poisoning: During experiments with the Warburg apparatus, Meier and Thoenes [5] made the observation that when to normal hepatic tissue a solution of racemic sodium lactate was added the respiratory quotient decreased, presumably because in the process of formation of dextrose the sodium ions are liberated and are free to combine with carbon dioxide. On the contrary, in similar experiments with livers from guinea-pigs treated with phosphorus the respiratory quotient remained unchanged. From this point of view it seemed interesting to follow the blood sugar of normal and poisoned rabbits after the administration of tolerance doses of lactic acid.

Lactic acid was given by stomach tube in the form of sodium lactate solution obtained by neutralization of normal lactic acid with 30 per cent sodium hydroxide. The dose was 2 Gm. per kilogram of body weight, the largest amount tolerated by rabbits without causing a rise of blood sugar, according to the work of Cori and Cori.[6]

These experiments were carried out on two animals. In rabbit 833 a three hour blood sugar curve after sodium lactate showed no rise of the blood sugar above the initial level. The average blood sugar during this time was 8 mg. lower than that taken before the administration of sodium lactate. When the toxic stage was reached, characterized by hypoglycemia during the last two hours of the tolerance test, the experiment was repeated. This time there was a moderate rise in the curve after sodium lactate, and the average blood sugar was 10 mg. above the initial value.

In a second rabbit (831) the first experiment with sodium lactate was performed as soon as the animal regained its ability to react to epinephrine after the administration of phosphorus was discontinued. This curve again showed practically no rise over the initial level and an average blood sugar that was 4 mg. below that at the beginning of the test. Injections of phosphorus were resumed, and three days later a curve after the administration of sodium lactate was obtained. This

5. Meier, R., and Thoenes, E.: Unpublished experiments.

6. Cori, C. F., and Cori, G. T.: Glycogen Formation in the Liver From D- and L- Lactic Acid, J. Biol. Chem. **81**:389, 1929.

curve exhibited considerable hyperglycemia, with its peak at the one hour period and elevation of the average blood sugar over the initial value amounting to 32 mg. The response to epinephrine at this time was reduced but still present. Two days later the experiment was done again, with the result that a similar hyperglycemic curve was observed, which had its peak at the three hour period. The average blood sugar was 30 mg. above the initial level. The corresponding curve after the administration of epinephrine this time showed hypoglycemia.

3. Recovery Experiments: On four occasions in three rabbits the administration of phosphorus was discontinued after hypoglycemia had appeared in the second part of the curve. In one of these animals (831) the hyperglycemia after the administration of epinephrine reappeared once after one day and once after two days of rest from injections of phosphorus. Another rabbit (833) regained its capacity to react to this hormone in two days. In the third animal (741) the hypoglycemia was markedly lessened after two days. Coincidentally, the three hour blood sugar curves, which were made only for the two last animals, showed their peaks again at the half hour period as normally. As additional signs of recovery in the second rabbit, the initial blood sugar had increased; the blood sugar level at the two and three hour periods had become lower than the initial blood sugar, and the average blood sugar was reduced.

When the injections of phosphorus were renewed, the typical hypoglycemia reappeared after a single injection in the animal in which only one injection was left out. In the rabbits in which two consecutive doses of phosphorus were omitted it required, respectively, nine and thirteen injections before the characteristic hypoglycemia was again observed.

Pathologic Data.—The livers of two rabbits (748 and 774) killed after four daily doses of phosphorus (corresponding to the first stage of our observations) were examined, and fatty degeneration of the cells around the portal spaces was found extending about half way to the central veins. Furthermore, in one of these animals hyaline cells were scattered irregularly through the lobules.

Livers of four animals at the terminal stage were examined microscopically. Two of these (740 and 828) were killed after having shown a hypoglycemic curve, and two (735 and 816) died spontaneously. The histologic picture of all four livers was essentially alike. There was very little fat present, but that small amount was diffusely scattered in small droplets. Most parenchyma cells were very young and exhibited evidence of rapid proliferation. They were irregularly placed without the usual trabecular arrangement. The nuclei showed no degeneration.

Finally, one rabbit (741) that died nine days after the last dose of phosphorus showed the same microscopic appearance of the liver and, moreover, marked congestion of the whole parenchyma with extravasation of blood around the central veins.

ACUTE PHOSPHORUS POISONING

As a check on certain phases of the work with chronic phosphorus poisoning several rabbits were given single doses of 4.5 mg. of phosphorus per kilogram of body weight. Two of these rabbits were alive twenty-four hours later, but were found dead thirty-six hours after the injection. Two more animals were killed for observations on the hepatic glycogen. Three of the rabbits that received single large doses of phosphorus were subjected fifteen hours later to the sugar tolerance and epinephrine tests. The obtained data are given in table 4. Figures

TABLE 4.—*Blood Sugar Curves after the Modified Dextrose Tolerance Test and the Administration of Epinephrine to Rabbits Subjected to Acute Phosphorus Poisoning*

	Blood Sugar After 5 Mg. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose, Water and Insulin	Difference Between Average Blood Sugar for 3 Hr. and the Initial Count	Average Blood Sugar for 2 Hr. After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr.
No.	Initial	½ Hr.	1 Hr.	2 Hr.	3 Hr.	3½ Hr.	4 Hr.	4½ Hr.	5 Hr.				
803	86	90	72	76	65	47	54	32	36	77	— 9	46	— 19
811	122	209	220	140	137	392	338	367	346	170	+48	335	+198
819	108	119	148	140	108	Animal killed				131	+23		

on the glycogen content of the liver before and after the modified dextrose tolerance test are given in table 3. From this it is seen that the initial blood sugar in all three rabbits was markedly lowered. In one animal (811) the three hour curve showed a remarkable hyperglycemia. In another rabbit (819) the average blood sugar level was also considerably higher than the initial value. In the third animal (803) there was practically no elevation of the blood sugar after dextrose, water and insulin had been given, and the average blood sugar was very low. But the difference between the latter and the initial blood sugar was the same as before poisoning. In the two curves in which the elevation of blood sugar took place, the peaks were at the one hour period, and the two hour blood sugar was above the initial one.

After epinephrine the blood sugar in the first animal rose in thirty minutes from 137 mg. to a maximum of 392 mg. and remained very high. Conversely, in the third rabbit the blood sugar fell to a very low level (32 mg.) and remained low, without causing convulsions.

The hepatic glycogen in one rabbit was found to be 4 per cent. After administration of dextrose, water and insulin it averaged 2.36 per cent in two animals.

Pathologic Examination.—Two rabbits in this series were examined pathologically, fifteen and eighteen hours, respectively, after the injection of phosphorus. Histologically, the liver of animal 817 showed nothing abnormal except vascular engorgement, while that of 819 exhibited beginning diffuse fatty infiltration which was most marked a little distance from the portal spaces. The livers of two rabbits that were found dead thirty-six hours after the injection were also studied. In one animal (803) extensive fatty degeneration involved most of the lobules except two or three rows of cells surrounding the central veins, where the fat droplets were less numerous. In addition, the parenchymatous cells were hyalinized and often exhibited pyknotic nuclei. The liver of animal 811 presented a picture of widespread necrosis with hemorrhages involving the entire parenchyma but leaving a thin fringe of intact cells arount the portal spaces. All cells were heavily laden with fat.

COMMENT

Chronic Phosphorus Poisoning.—In considering the significance of these experimental findings two facts must be constantly borne in mind. The first is that the principal function of the liver in its relation to carbohydrate metabolism, as emphasized by Fischler,[7] is the maintenance of a constant blood sugar level. The second is that while practically all investigators of the action of phosphorus and chloroform concur in the opinion that the liver is the only organ seriously damaged by these substances, there are other factors concerned in the utilization of carbohydrates which, by exercising a compensatory function in hepatic insufficiency, may modify the effect of injury to the liver without direct action of these poisons on other organs.

In reviewing the influence of chronic phosphorus poisoning on rabbits, we see that as early as four days after the beginning of injections of phosphorus the initial blood sugar and the glycogen content of the liver were considerably lowered. Thereafter, the initial blood sugar remained low until death. In other words, from the beginning evidence points to a deficiency of the chief function of the liver, that of maintaining a certain optimum blood sugar level. The same observation was made by Mann[8] on dogs with partial hepatectomies. Drastic lowering of the blood sugar level after phosphorus poisoning in man

7. Fischler, F.: Physiologie und Pathologie der Leber, Berlin, Julius Springer, 1925, p. 65.

8. Mann, F. C.: The Effects of Complete and Partial Removal of the Liver, Medicine **6**:420 (Dec.) 1927.

was reported by McIntosh [9] and by McLean, MacDonald and Sullivan.[10] Experimental results that conflict with ours may be explained, at least in cases in which rabbits were used, as suggested in our preliminary experiments, by lowering of the blood sugar in the controls through over-night fasting.

As poisoning with phosphorus progressed, the sugar tolerance of our rabbits was gradually reduced. In reference to the shape of the curve, the manifestations of diminution in dextrose tolerance on the fifth day were a relatively higher peak at the normal time and a slower return of the blood sugar to the initial level. On the ninth day the blood sugar continued to rise during the entire first hour, and on the eleventh day in three of the six rabbits the blood sugar reached its maximum only at the two hour period.

Quantitatively, up to the ninth day of poisoning the average blood sugar for three hours was below normal, due to the low initial blood sugar level, but the increase of the average blood sugar over the initial level was considerably greater than the normal for the same animals. From the tenth day on, both the average and, more strikingly, the increase of the average over the blood sugar at the beginning of the test were greater than before the administration of phosphorus. The explanation for this reduced sugar tolerance is at least partially supplied by the fact that the glycogen content of the livers of these animals is somewhat reduced instead of being increased after administration of dextrose, water and insulin.

The work of Mann and Bollman [11] with partial hepatectomies shows that reduced capacity of the liver can be responsible for a delayed rate of disappearance of sugar from the blood. Von Noorden and Isaac,[12] among others, mentioned the higher and more prolonged rise of the blood sugar after the administration of dextrose in patients with hepatic disease. It must be remarked here that the last observation holds true only for group averages. In many cases of even advanced diseases of the liver, the sugar tolerance is found to be still within the upper limits of normal. On the other hand, in the present study injury to the pancreas and voluntary fasting by the indisposed animals must be ruled out as possible causes of reduced sugar tolerance.

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9. McIntosh, R. M.: Acute Phosphorus Poisoning, Am. J. Dis. Child. **34**: 595 (Oct.) 1927.

10. McLean, S. A.; MacDonald, A., and Sullivan, R. C.: Acute Phosphorus Poisoning from the Ingestion of Roach Paste, J. A. M. A. **93**:1989 (Dec. 7) 1929.

11. Mann, F. C., and Bollman, J. L.: Liver Function Tests, Arch. Path. & Lab. Med. **1**:681 (May) 1926.

12. von Noorden, C., and Isaac, S.: Die Zukerkrankheit und ihre Behandlung. Berlin, Julius Springer, 1927, p. 42.

Besides the histologically demonstrated relative immunity of the pancreas to phosphorus, the uniformly low initial blood sugar in all stages of poisoning speaks strongly against any considerable damage of this organ in our rabbits. The hypoglycemia that commences three and one-half hours following the modified dextrose tolerance test, when a certain stage of phosphorus poisoning is reached, also argues against an insufficiency of insulin.

The possibility that voluntary fasting lowered the sugar tolerance of the rabbits appears unlikely, because, except for the last two or three days before death, the animals showed no change in their habits of eating. Moreover, a similar decrease of sugar tolerance was observed in our acute experiments when the animals were tested twelve hours after the injection of a large dose of phosphorus. It is evident that under these conditions fasting played no part.

Observations on a rabbit (833) in the most advanced stage of phosphorus action showed very little rise in blood sugar after the administration of dextrose, water and insulin given six hours before death. However, the average blood sugar in contrast to that found in the same animal in the normal state was still higher than the initial blood sugar. This terminal increase in sugar tolerance, if real, has its counterpart in the greater rate of disappearance of dextrose injected into totally dehepatized dogs and is interpreted by Mann and Bollman [11] as being due to loss of the regulatory action of the liver. On the other hand, in our animal it might also have been caused by poor absorption from the alimentary canal in view of impending dissolution.

The epinephrine hyperglycemia of our rabbits was greatly increased four days after the beginning of injections of epinephrine. Two days later it was still increased, but less in two animals, and it was decreased in one. In addition, there was at this stage in all animals a delay in the action of epinephrine, as shown by curves that reached their peaks in the last blood sample. On the ninth day the response to epinephrine was below normal, and the delay of its action had found additional expression in a continuation of the fall in blood sugar during the first thirty minutes after the injection.

Starting on the tenth day of poisoning in one rabbit, on the eleventh day in four and on the sixteenth day in another, no increase but a fall in blood sugar after the administration of epinephrine took place (see the accompanying chart). Two rabbits died without having been observed in this hypoglycemic stage. One of these (735) had only a slight epinephrine hyperglycemia on the ninth day and died six days later without further tests having been made. The other animal (816) exhibited reduced and delayed response to epinephrine on the eleventh day, and succumbed two days later without further observations having been made. In both rabbits daily injections of phosphorus were con-

tinued until death, and it is highly probable that the characteristic hypoglycemia was missed, because no tests were made during the last days of life.

Two of the six rabbits (831 and 833) for which the hypoglycemic curves after the injection of epinephrine had been observed were permitted to recover, the injections of phosphorus being stopped. When poisoning was resumed, both animals again exhibited lowering of the blood sugar following the administration of epinephrine.

From the observed facts it is seen that at first small doses of phosphorus act as an irritant to the glycogenolytic mechanism of the liver and similarly to thyroxine, rendering the liver more susceptible to the action of epinephrine in spite of a marked reduction in hepatic glycogen. This phase of our study confirms the conclusion that Macleod [13] drew from the results of experiments with thyroxine: "that it is not alone the percentage of glycogen in the liver that determines the readiness with which this organ may discharge sugar into the blood, but also the sensitivity of the glycogenolytic mechanism." Whipple, Peightal and Clark,[14] who reported hypersecretion of phenoltetrachlorphthalein by the liver after small doses of phosphorus, also looked for an explanation to the irritative effect of this drug on the secreting parenchyma—a stage perhaps preceding that of actual injury or necrosis of the cells.

For better understanding of this phenomenon, it was necessary to determine whether the hypoglycemia described, which was observed in eleven curves made for six rabbits, was caused by epinephrine or whether it took place in spite of it. Observations of the blood sugar over five hours with the modified dextrose tolerance test without epinephrine being given in two rabbits (831 and 833) showed that epinephrine was not responsible for the hypoglycemia. On the other hand, this hormone was impotent to prevent its occurrence or even to diminish it.

Mann and Magath [15] demonstrated that extirpation of the liver prevented hyperglycemia after the administration of epinephrine, and that there was not even a temporary delay in the steady fall of blood sugar in dogs. In demonstrating the dependence of post-epinephrine hyperglycemia on the functional activity of the liver, the present experiments possess the advantage that the action of epinephrine was abolished

13. Macleod, J. J. R.: The Physiology of Glycogen and the Rôle of Insulin and Epinephrine in Carbohydrate Metabolism, Lancet **2**:1 (July 6) 1929.

14. Whipple, G. H.; Peightal, T. C., and Clark, A. H.: Tests for Hepatic Function and Disease Under Experimental Conditions; Phenoltetrachlorphthalein, Bull. Johns Hopkins Hosp. **24**:343 (Nov.) 1913.

15. Mann, F. C., and Magath, T. B.: Die Wirkungen der totalen Leberextirpation, Ergebn. d. Physiol. **23**:212, 1924.

in rabbits in which the blood sugar following a period of hypoglycemia was able to return spontaneously to its previous level, and that the animals in which this occurred were still capable of prompt recovery at the cessation of injections of phosphorus.

The fact that phosphorus poisoning prevents the hyperglycemic action of epinephrine is difficult to reconcile with the view that decreased utilization of blood sugar by the tissues is the principal cause for hyperglycemia after the administration of this drug under postabsorptive conditions. If this were true, why should hepatic damage in animals in the postabsorptive stage nullify the action of epinephrine?

The genesis of the hypoglycemia that occurred so regularly at a certain stage of phosphorus poisoning is especially interesting to us because of its similarity to the hypoglycemia observed in human cases of hepatic disease following the modified dextrose tolerance test. We know that the main mechanism by which a nearly constant blood sugar level is maintained in the normal animal is the secretion of insulin, which increases the utilization of sugar by tissues when hyperglycemia begins to appear, and the release of dextrose from the glycogen stores of the liver when a certain degree of hypoglycemia is reached. This balance is demonstrated in the ordinary dextrose tolerance test by a fall of the blood sugar curve below the initial level toward the end of the test and by a secondary rise which follows this fall.

In late phosphorus poisoning the ability of the liver to release dextrose is abolished, as was demonstrated by the experiments with epinephrine. In consequence, the downward course of the blood sugar continues unchecked until the stimulus furnished by the dextrose absorbed from the intestine is exhausted. In this manner marked hypoglycemia is produced following the initial hyperglycemia. The injection of insulin and the administration of water along with the feeding of dextrose in the modified dextrose tolerance test intensify this fall in blood sugar. In addition, it is probable that with the onset of hepatic insufficiency the tissues and the pancreas take a larger part in the disposal of absorbed carbohydrates, thus increasing still further the tendency to terminal hypoglycemia.

Before we leave the subject of chronic phosphorus poisoning, it seems interesting to point out the comparatively normal appearance of the hepatic cells and the slight amount of fatty degeneration in the livers of rabbits that died or were killed in advanced stages of poisoning. This is the more unexpected since in earlier stages fatty degeneration is pronounced. The only important abnormalities of the liver found in late stages of chronic phosphorus poisoning are the loss of trabecular arrangement of the parenchymatous cells and their young appearance.

Acute Phosphorus Poisoning.—The results of the experiments with single large doses of phosphorus are confusing when taken alone, but

easily interpreted when viewed in the light of the changes produced by chronic poisoning. The initial blood sugar was lowered in all three rabbits. The two three hour curves that rose after the modified tolerance test are both indicative of reduced sugar tolerance. The third curve obtained in rabbit 803 which had lost its response to epinephrine is similar to the tolerance curve obtained shortly before death in the chronically poisoned animal 833. The epinephrine hyperglycemia was extreme in one case (811), indicating a short stage of irritation similar to the more protracted one in the animals subjected to chronic poisoning. The fact that the maximum elevation of the blood sugar was reached thirty minutes after the injection of epinephrine is additional proof of the lability of the glycogenolytic mechanism in this rabbit. The other animal (803), for which a post-epinephrine curve was obtained, already showed the typical hypoglycemia and lack of response to this hormone so characteristic of later stages of poisoning with small doses of phosphorus. Finally, the glycogen content of the liver was reduced, although to a lesser extent, and administration of dextrose, water and insulin, just as in chronic phosphorus poisoning, brought about a reduction, rather than an increase, in hepatic glycogen.

One may conclude from these observations that acute and chronic poisoning with phosphorus produce the same effects on sugar tolerance and epinephrine response. Since in the acute experiments the sequence of events is much faster, different degrees of functional impairment (depending on the rate of absorption of phosphorus, susceptibility of the individual animal, etc.) may be observed after the same number of hours following the injection of the poison. Individual differences in function found their counterpart in variations in the histologic picture observed in the livers of rabbits killed at the same period after the administration of equal doses of phosphorus.

Utilization of Lactic Acid in Phosphorus Poisoning.—Experiments with feeding of sodium lactate demonstrated that in advanced stages of phosphorus poisoning hyperglycemia is produced with amounts of sodium lactate that were previously tolerated without elevation of the blood sugar. Moreover, the peak of the hyperglycemic curve fell into a later period as poisoning progressed, just as after tolerance tests with dextrose. These results indicate that lactic acid is still converted into dextrose after the liver becomes unable to release a sufficient amount of sugar from glycogen in response to the stimulus of hypoglycemia and of epinephrine. However, the dextrose produced is subject to the same delayed utilization as the sugar absorbed from the gastro-intestinal tract.

The fact that the liver retains its capacity to change lactic acid into dextrose in late stages of phosphorus poisoning permits the cycle of blood sugar → muscle glycogen → lactic acid → blood sugar to continue

even in the apparent absence of glycogen formation. This and probably dextroeogenesis explain the survival of our rabbits during the last stage of this experiment and also furnish a keq to the understanding of the mechanism by which the low blood sugar induced by the modified tolerance test slowly returned to its previous level after failing to show an increase following the injections of epinephrine.

Recovery from Phosphorus Poisoning.—The prompt recovery of the rabbits when administration of the phosphorus was discontinued testifies that neither the hypoglycemia during the second half of the five hour curve nor the absence of the epinephrine response can be regarded as a terminal event in fatal cases of poisoning. So far as can be judged from the limited number of observations, hyperglycemia after the administration of epinephrine was the first condition to return in the recovering animals. Sugar tolerance and especially the initial blood sugar level were somewhat slower to recover.

After the administration of phosphorus was discontinued, the animals acquired resistance to further injections of this poison with extraordinary rapidity. When a single injection of phosphorus had been omitted, the injection following abolished the response to epinephrine. But when two injections were left out in one rabbit (833) it took as many, and in another case (831) even one and one-half times as many, injections as were required for the healthy animals in order to reach the same stage. Since we know from our tests of sugar tolerance and epinephrine response that the rabbits had not completely recovered when the second period of poisoning was started, it seems probable that the new cells of the liver at this particular stage were more resistant to phosphorus. This impression is also strengthened by the virtual absence of fatty degeneration in the young cells. It is of interest that Davis and Whipple [16] had the same experience in dogs with a temporary tolerance to chloroform immediately after recovery from the first dose. When the animals in their series were allowed to recuperate for two or three weeks, a tolerance to the second dose was not exhibited.

SUMMARY

Rabbits receiving small daily doses of phosphorus were subjected to a modification of the dextrose tolerance test followed by an injection of epinephrine. Blood sugar curves following these procedures and determinations of the hepatic glycogen before and after the modified dextrose tolerance test were made.

16. Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, Arch. Int. Med. **23**:612 (May) 1919.

The first functional deficiency of the liver to appear was a failure on the part of this organ to maintain the normal blood sugar level. Later, a progressive decrease in sugar tolerance was manifested which could be explained at least in part by lack of glycogen deposition in the liver following the administration of dextrose, water and insulin. In the last stages of poisoning after the modified dextrose tolerance test blood sugar curves ending in hypoglycemia were typical.

Epinephrine hyperglycemia in these animals was at first increased, then decreased, and finally abolished altogether. Thus the observed hypoglycemia is explained by failure of glycogenolysis to check the downward course of the blood sugar initiated by the stimulus of the ingestion of dextrose. An important additional factor probably is the compensatory rôle that the pancreas and the muscles play in the disposal of carbohydrates in case of hepatic insufficiency.

Even in late stages of phosphorus poisoning, the liver was found capable of transforming lactic acid into dextrose.

The experiments with acute phosphorus poisoning gave results very similar to those of chronic phosphorus poisoning.

SOLAR RADIATION IN RELATION TO ENDEMIC GOITER

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I. THE RELATION OF SOLAR RADIATION TO THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN THE UNITED STATES

In the preparation of another paper [1] dealing with pellagra, in which the relative deficiency of solar rays in winter seemed to have a conditioned relationship to the distribution of pellagra, it was noted that the pellagra area in the United States, broadly speaking, ends where the area of endemic goiter begins, and that deficiency of winter sunshine is more marked in the goiter area than in the pellagra area. A somewhat similar relationship in the geographical distribution of the two diseases may be seen also in Europe and Asia. Southwest Virginia appears to be one of few areas of the earth's surface where endemic goiter and endemic pellagra meet on common ground, and in this area the prevalence of each is only moderate. This section deals with the correlation of deficiency in solar radiation and presence of endemic goiter, and seeks to present from the literature certain data suggestive of mechanisms possibly relating the two.

Probably no one now questions the influence of iodine in the prevention of simple goiter. It is important to bear in mind, however, that the physiologic action of any substance necessary for the organism is a matter of its availability for tissue needs rather than any mere question of supply. Iodine supply must, therefore, be considered in the light of its absorption from the intestinal tract (or by other routes) as influenced by factors such as the p_H of the intestinal tract; the possibility of its premature excretion after absorption (retention as opposed to physiologic waste); its fixation with other substances that may render it unavailable for physiologic use (as with unsaturated fatty acids); its bound or unbound state, its diffusibility through membranes, the proportion in a state of ionization; the available supply in proportion to other substances with which maintenance of physiologic equilibrium is impor-

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1. Smith, J. H.: The Influence of Solar Rays on Metabolism: With Special Reference to Sulphur and to Pellagra in Southern United States, Arch. Int. Med. **48**:907 (Nov.) 1931.

tant (as possibly calcium),[2] and the condition of special tissues such as the thyroid gland to use the available iodine for specific purposes such as the manufacture of thyroxine and the storage of colloid. Thus it is seen that the available iodine may vary from the ingested iodine.

Marine[3] held that while goiter is apparently always due to a deficiency of iodine in the thyroid gland, the deficiency may be primary or absolute on the one hand, and secondary or relative on the other hand. Of the causal factors that have been suggested, Marine considered that water, poverty, damp sunless habitations and especially diet are of general importance today. Water, food and, through food, poverty are recognized modes of iodine deficiency. It is with the other factor, damp, sunless habitations, that this article chiefly deals.[4]

The elusive quality of the relationship of iodine to the thyroid gland is fully attested in many places. McClendon,[5] in reviewing the iodine determinations of drinking water from the State of Utah made in his laboratory, found that there was not a very close relationship between iodine and freedom from goiter. The iodine content of the same water supply was found to vary at different times. The water supply of Stanford University varied considerably during different months. It

2. D. Marine (Ann. Int. Med. **4**:423, 1930) referred to the physiologic action of glutathione and other substances important in the reduction-oxidation processes of the organism as having possible goitrogenic influence. Practically all experiments and observations relating to the etiology of goiter result in recognition of the fact of an unexplained susceptibility in certain persons, leading the observer to postulate a "constitutional factor" (Webster, B., and Chesney, A. M.: Am. J. Path. **6**:275, 1930). The feature of inheritance has been emphasized time and again, but comparatively little attention has been paid to the effect on inheritance produced by an early change of environment.

3. Marine, D.: Studies on the Etiology of Goiter, Including Graves' Disease, Ann. Int. Med. **4**:423, 1930.

4. "Bad hygiene" has been considered a cause of goiter. McCarrison (McCarrison, B., and Newcomb, C.: Indian J. M. Research **17**:1061, 1930), defining this vague term for rats as "dirty cages," concluded that unhygienic conditions of life could cause simple hypertrophic goiter in these experimental animals. Since the control "clean cages" were submerged at intervals in boiling water, involving transfer of the animals, it would appear that environmental factors other than the condition of the cages might have to be evaluated. Excreta of rats are not always harmful to other rats, and in some circumstances may be actually beneficial. Nelson and Steenbock (quoted by Laurens, H.: Physiol. Rev. **8**:57, 1928), showed conclusively that when irradiated and nonirradiated rats are kept in the same cage, the stimulation to growth exerted on the nonirradiated rats is mediated by their consuming the antirachitically activated excreta of the irradiated animals. Webster and Chesney (Am. J. Path. **6**:275, 1930) found that there was no greater tendency to thyroid hyperplasia when rabbits were kept under conditions permitting easy contamination of food than when they were maintained in special cages under the best possible conditions.

5. McClendon, J. F.: Iodine and Goiter in Utah and Use of the Cottrell Precipitator in Iodine Analysis, Proc. Soc. Exper. Biol. & Med. **23**:494, 1926.

does not seem that any adequate investigation has been made of the possibility that solar irradiation may be one influence in these variations and in the features of goiter epidemiology noted in the following paragraph:

Numerous authors have cited examples of rivers and streams which, although "goitrigenous" at their source, lose this property during their course, and vice versa.[6] Following a change of the source of water supply of towns and cities in the United States, the new supply coming from neighboring mountains (Oregon and Washington,[7] St. George, Utah [8]), in some instances in which the water supply is piped from mountain springs (Lewistown, Mont.[9]), a relatively high incidence of goiter is reported. In Utah, Middleton [8] described the earlier source of supply as wells and water from surface springs. In Virgin Valley, Utah (without reference to the source of the water supply), Middleton found a very high incidence of goiter and encountered enormous thyroid growths in the isolated mountain gorges. In Montana, Foard [9] found that similar conditions—proximity to mountains, isolation, well and surface spring water—were associated with goiter endemicity second in degree only to the piped water supply from a mountain spring supplying Lewistown. In connection with several reported epidemics of goiter, notation was made of an unusually cloudy, rainy or stormy season.[10]

Consideration will now be given to certain data suggesting that iodine metabolism and the size of the thyroid gland may be influenced by irradiation of water, food or the skin of the animal organism, and that such an influence may be exerted either directly or through the well established power of ultraviolet irradiation to alter calcium metabolism.

Hess and Lundagen [11] demonstrated a seasonal variation in the level of the inorganic phosphate of the blood of normal infants which corresponds to and is determined by the seasonal variation in the richness of the solar spectrum in ultraviolet rays. Tisdall and Brown [12] showed an increase in bone ash from ultraviolet irradiation of rats on a rachitogenic diet. Increased p_H of the intestinal contents tends to inhibit the absorption of calcium, and under these conditions ultraviolet irra-

6. Crotti, A.: Thyroid and Thymus, ed. 2, Philadelphia, Lea & Febiger, 1922, p. 269.

7. Olesen, R.: Endemic Goiter in Oregon, Pub. Health Rep. **42**:2831, 1927.

8. Middleton, G. W.: Goiter in the Intermountain Region of Utah, J. A. M. A. **84**:1172 (April 18) 1925.

9. Foard, F. T.: Thyroid Enlargement Among Montana School Children, Pub. Health Rep. **39**:2354 (Sept. 12) 1924.

10. Crotti, A.: Thyroid and Thymus, ed. 2, Philadelphia, Lea & Febiger, 1922.

11. Quoted by Laurens, H.: Physiol. Rev. **8**:57, 1928.

12. Tisdall, F. F., and Brown, A.: Relation of the Altitude of the Sun to Its Antirachitic Effect, J. A. M. A. **92**:860 (March 16) 1929.

diation promotes absorption and retention of both calcium and phosphorus (Grayzel and Miller [11]). These rays may also convert a latent into an active tetany.[13] These observations, bearing on rickets, are introduced for the purpose of emphasizing that the relationship between ultraviolet irradiation and calcium metabolism is not confined to rickets, and for the purpose of comparison with other data to be referred to later in which iodine appears to be a substitution factor for ultraviolet radiation in the growth and maintenance of the weight of animals.

Laurens [14] found:

> . . . an unexpected similarity between the effects of change from roomlight to darkness and vice versa, and the effects following irradiation. There is in both a stimulation of endogenous nitrogen metabolism resulting in a decrease in the balance. . . . Probably any deviation from the usual so far as radiant energy is concerned, acts as a stimulus which disturbs the metabolism of nitrogen, calcium and phosphorus. The antirachitic factor (vitamin D, either absorbed from the intestinal tract or produced by irradiation of the skin) works not only in the retention of calcium in rickets but also in the adult in which rickets is never observed. It represents specifically the organic agent which promotes normal calcium anabolism. It may cure rickets, it may promote growth, or it may simply prevent excessive loss of lime from the body. Irradiation revives a depressed function.

Goldblatt and Soames [11] found that irradiation of rats on a rachitic diet had a positive influence in maintaining weight and growth. Laurens and Sooy [11] got similar results in albino rats on a normal diet. Hanzlik, Talbot and Gibson [15] found that the administration of iodide had an effect similar to that just described for irradiation in maintaining the weight and growth of rats both on complete dietary and on a rachitic diet.

Independent of any known association with calcium metabolism, the goitrogenic effect of certain foods appears to be subject to seasonal variations possibly dependent on the solar irradiation of growing vegetables. Following the report of Webster and Chesney [16] that cabbage appeared to have a goitrogenic effect in rabbits, Marine, Baumann and Cipra [17] further investigated the conditions of this result. Among other

13. Cantarow, A.: Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1931; footnote 11.

14. Laurens, H.: The Physiological Effects of Radiation, Physiol. Rev. **8**:57, 1928.

15. Hanzlik, P. J.; Talbot, E. P., and Gibson, E. E.: Continued Administration of Iodide and Other Salts: Comparative Effects on Weight and Growth of the Body, Arch. Int. Med. **42**:579 (Oct.) 1928.

16. Webster, B., and Chesney, A. M.: Studies in the Etiology of Simple Goiter, Am. J. Path. **6**:275, 1930.

17. Marine, D.; Baumann, E. J., and Cipra, A.: Studies on Simple Goiter Produced by Cabbage and Other Vegetables, Proc. Soc. Exper. Biol. & Med. **26**:822, 1929.

modifying influences, they found that so-called summer cabbage had a much less marked goiter-producing tendency than cabbage grown in the late autumn, so-called winter cabbage. Cabbage and other Brassicae were found to have both a goitrogenic and an antigoitrogenic factor. Marine and his collaborators affirmed that the possibility that thyroid hyperplasia due to feeding cabbage is dependent on an absolute deficiency of iodine can be dismissed. Webster and Chesney [16] noted that rabbits brought into their laboratory in the late fall or winter developed goiter on a cabbage diet much more promptly than those brought in during the spring and summer. Similarly, some of the large goiters tended to decrease in size slightly during the spring and summer. Webster, Clawson and Chesney [18] found that in goitrous rabbits the average production of heat was 16.6 per cent lower than in "normal" rabbits; those with the largest goiters showed the greatest depression in metabolic rate; the rate was practically constant in individual goitrous animals over a period of one year, provided there was no great change in the size of the gland. There was, however, a tendency, as stated, for the glands to decrease in size during the spring and summer.

The direct effect of irradiation on iodine metabolism has been studied by Pincussen and Roman.[19] These investigators found that rabbits to which potassium iodide had been administered by mouth, when later exposed to high mountain sunshine at Davos, Switzerland, showed a greatly increased excretion of nitrogen. Further, accepting as established and as a basis for a series of experiments the fact that iodine water solution under the influence of light gives off iodine, they reported the following results: In white mice, by irradiation with the mercury quartz lamp, in both normal animals and animals into which injections of inorganic iodine had been made, the proportion of organic to inorganic iodine decreases, and there is an increase of dialyzable iodine at the expense of the organically bound iodine.[20]

The seasonal variations in the goitrogenic properties of cabbage and the influence of light on the ionization and diffusibility of iodine in water and animals are suggestive only as to the influence of light on the available iodine supply for the thyroid gland of the human population of a given area.

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18. Webster, B.; Clawson, T. A., and Chesney, A. M.: Endemic Goiter in Rabbits: II. Heat Production in Goitrous and Non-Goitrous Animals, Bull. Johns Hopkins Hosp. **43**:278, 1928.

19. Pincussen, L., and Roman, W.: Effect of Irradiation on Iodine and Bromine Fractions in Animal Organism, Particularly Following Administration of Salts of Iodine, Biochem. Ztschr. **216**:336, 1929.

20. Clark (The Physiological Action of Light, Physiol. Rev. **2**:277, 1922) has shown a similar result, an increase in diffusible calcium of serum irradiated in quartz test tubes.

There is evidence to suggest that an increased intake of calcium may result in an increased requirement of iodine. McCarrison,[21] in Southern India, at an altitude of 6,000 feet, found that the effect on the thyroid gland of pigeons and rats of the excessive ingestion of lime, for a period of eight and a half months (from October to June), was to cause in certain individuals an increase in size of the organ of approximately 50 per cent. This increase was due to the abnormal accumulation of colloid material in the vesicles of the gland. There was no associated hyperplasia of the organ. The undue accumulation of colloid was preventable by increasing the intake of iodine proportionately to the excessive ingestion of lime. McCarrison concluded that a balanced adjustment of lime and iodine in the diet would appear to be necessary for the normal storage and resorption of colloid material by the thyroid gland, and that this observation would appear to have a bearing on the pathogenesis of colloid goiter in man.

There are recorded [10] instances of goiter endemicity on one bank of a stream and its absence on the other, corresponding to limestone and its lack. Lobenhoffer [22] affirmed that the intrusion of small wedges of shelly limestone amidst other formations will invariably augment the intensity of the goiter endemic. But it is not possible to generalize with regard to the distribution of calcium and its relation to iodine. The earlier tendency to general statements in the literature with reference to the iodine content of water, soil and vegetables has been followed by the report of striking exceptions and contradictions, as at Provincetown, Cape Cod, Mass.,[23] Marshfield, Ore.,[23] Mt. Clemens, Mich.,[24] Utah,[25] and in the vegetables of South Carolina, where the iodine content of vegetables appears to increase with distance from the sea.[26]

The tendency of goiter areas to be limited to the geological formations of the last glacial deposits has often been emphasized. So far as goiter tends to be endemic in mountainous countries, the following quotation fixes also the relation of goiter territory to the glacial deposits referred to. The Encyclopaedia Britannica (fourteenth edition) speaks

21. McCarrison, R.: The Effects of the Excessive Ingestion of Lime on the Thyroid Gland and the Influence of Iodine in Counteracting Them, Indian J. M. Research **13**:817, 1925-1926.

22. Quoted by Crotti (footnote 10).

23. Olesen, R.: Endemic Goiter Among School Children, Pub. Health Rep. **42**:3180 (Dec. 30) 1927.

24. Olin, R. M.: Iodin Deficiency and Prevalence of Simple Goiter in Michigan, J. A. M. A. **82**:1328 (April 26) 1924.

25. McClendon, J. F.: The Distribution of Iodine with Special Reference to Goiter, Physiol. Rev. **7**:189, 1927.

26. Weston, W., and Remington, R. E.: The South Carolina Food Research Commission: Preliminary Report on Its Organization and Activities, J. A. M. A. **92**:2161 (June 29) 1929.

of "the great extension of glaciers in almost every mountain center of the world in recent geological time." In more detail, endemic goiter territory tends to extend down mountain slopes into valleys and moraines and out on to plateaux at the base of mountains to conform to glacial movements. Further, in certain instances in which goiter occurs conspicuously in nonmountainous countries, as around the Great Lakes and in the St. Lawrence Valley of North America, still the goiter area overlies the more recent glacial deposits. The significance of this correlation has never been established in terms of chemistry. There is considerable evidence that the areas described are areas of low iodine content of soil and water, but there are many exceptions among the reported analyses. Indeed, it is not certain that deficiency in iodine is a more constant characteristic than high calcium content of the soil and water in the area of glacial deposits so far as the references consulted show. For the present it would seem more likely that the ultimate understanding of the etiology of goiter will explain its occurrence in the regions of glacial deposits rather than that the overlying of the two areas will explain the etiology of goiter.

If it is tentatively assumed that lack of sunshine in winter is a contributing factor to goiter endemicity, it is not difficult to show how this factor may be intensified in several ways, the total intensity applying inclusively though somewhat variably to water, home grown food and the organism directly.

The decreased angle of incidence of the sun's rays on the earth's surface in winter is a matter of common knowledge, and the decrease varies directly with proximity to the Arctic Circle. However, the air mass penetrated by the sun's rays does not vary directly with latitude, but is greatly exaggerated by proximity to the Arctic Circle.[1] Moreover, the days are short.

Water vapor has a measurable influence on the depletion of ultraviolet wavelengths and on the total radiation in solar rays.[27]

The decreased winter temperatures and snows of northerly latitudes tend to close housing, especially of the female population, accentuated by isolated living conditions.

The topography of the country has a relation to solar radiation also. Though the intensity of ultraviolet radiation may be increased at high altitudes, and though weather observation stations may record a high percentage of the possible sunshine, neither takes into account the deprivation involved in a rugged terrain. The observations of weather bureau stations are, therefore, a better index of the solar irradiation of

27. Kimball, H. H.: The Distribution of Energy in the Visible Spectrum of Sunlight, Skylight and the Total Daylight, International Commission on Illumination, September, 1928.

flat countries than of the much shadowed surface area of mountainous countries. Undoubtedly, if the observation is valid, the implication is that goiter is more frequent on the shaded slopes of mountains, in a manner comparable to the woodsman's guides as to the points of the compass. While there are frequent references to goiter in valleys and

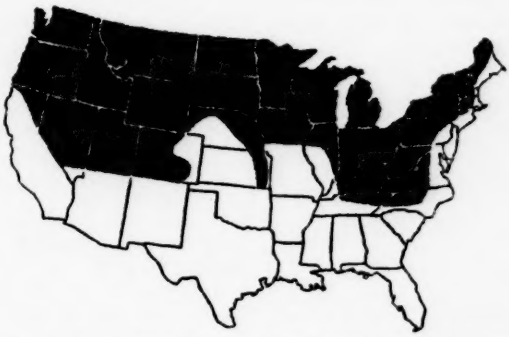

Chart 1.—The iodine in drinking water in the United States. In the black area, waters contain from 1 to 22 parts of iodine per hundred billion parts of water; in the white area, from 23 to 18,470 parts. (After McClendon, J. F., and Hathaway, J. C.: Inverse Relation Between Iodin in Food and Drink and Goiter Simple and Exophthalmic, J. A. M. A. **82**:1668 [May 24] 1924.)

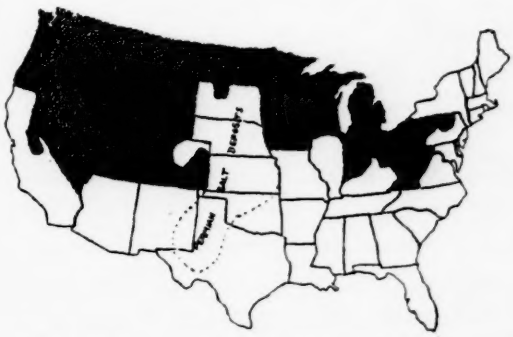

Chart 2.—Simple goiter in the United States, from data of the Draft Board. In the white area, there were from 0 to 5 military goiters per thousand drafted men; in the black area, from 5 to 111. (After McClendon and Hathaway.)

mountain gorges, no recorded observation for or against its association with shaded slopes has been noted. The prevalence of goiter in mountainous countries, even in the tropics, is generally accepted, but it is difficult to appraise the comparative influence of climatic and geological factors with their implied chemical, and possibly other, significance.

Charts 1 and 2, respectively, reproduce McClendon and Hathaway's maps of iodine in drinking water in the United States and simple goiter in the United States from data of the Draft Board. Chart 3 illustrates the distribution of iodine according to McClendon's figures [25] and tends to confirm the observation of McClendon [5] that there is not a very close relationship between iodine and freedom from goiter.

Chart 4 illustrates the fact that endemic goiter is hardly a problem in states below latitude 37° 30′ N. In the northwest, the correlation

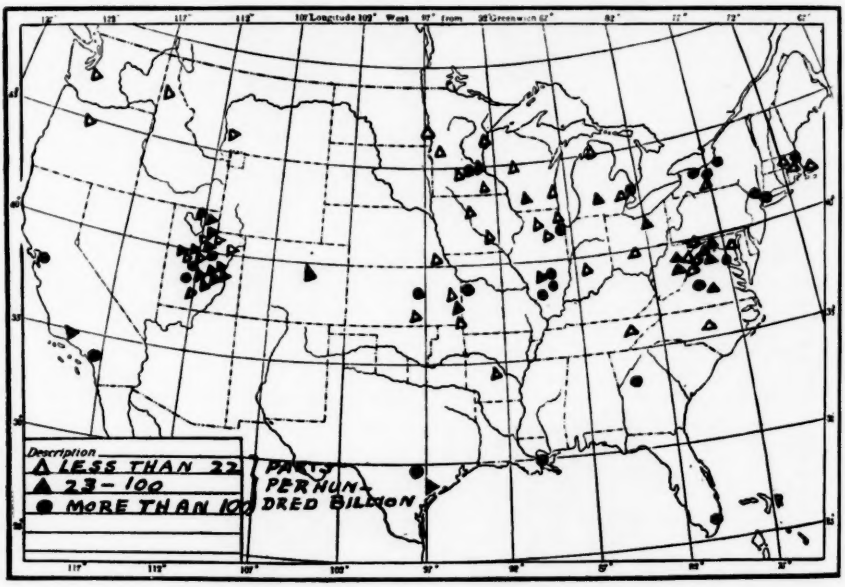

Chart 3.—Iodine in the drinking water in the United States. (After McClendon, footnote 25.)

between goiter endemicity according to the data of the Draft Board and lack of winter sunshine is fairly close. If the figures for school girls reported in special surveys are considered, goiter is more prevalent in the area about the Great Lakes than in the Pacific Northwest, and the greatest prevalence corresponds in both areas quite closely to the greatest deficiency in winter sunshine. This correlation between goiter prevalence and lack of sunshine appears to be fairly close for the United States generally north of about 37 degrees latitude. The observation would appear to have a possible bearing on the etiology of goiter and on the low iodine content of the thyroid gland in the early spring as reported

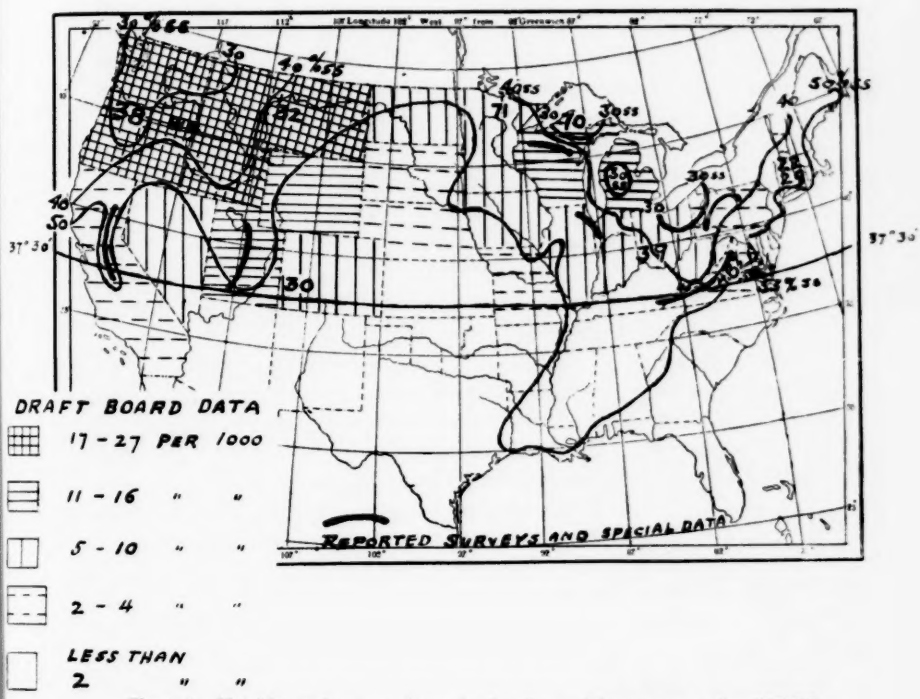

Chart 4.—Hatching values are shown in the chart. The curves, as for *30%SS*, indicate that the areas enclosed receive for the months of December, January and February an average of less than the indicated percentage of the possible sunshine according to data in Bulletin W of the United States Weather Bureau, covering the observation periods from the establishment of the stations to 1920, inclusive. The figures, as *53%SS*, within the State of Virginia are intended to show a percentage of the possible sunshine of 53 per cent for the coastal area; 52 per cent, tidewater; 48 per cent, Piedmont, and 45 per cent, mountain area. Other figures inserted within the boundaries of states represent the highest percentage of goiter found in school girls in any area of the state included in special surveys, and with the exception of the figure *39* for Cincinnati, the location of the figure within the state boundary indicates the area of greatest prevalence observed within the state. The heavy black inserts also have the same significance as to the relative prevalence within the state. The sources of these data are as follows: Oregon (Cascade Mountains), Olesen (Pub. Health Rep. **42**:2831, 1927); Montana (Rocky Mountains), Foard (Pub. Health Rep. **39**:2354, 1924); Colorado (Rocky Mountains), Public Health Report **40**:1, 1925; Minnesota, Olesen and Clark (Pub. Health Rep. **39**: 2561, 1924); Michigan, Olin (J. A. M. A. **82**:1328, 1924); Cincinnati, Olesen (Pub. Health Rep. **39**:1777, 1924); Connecticut, Olesen and Taylor (Pub. Health Rep. **41**:1685, 1926); Massachusetts, Olesen and Taylor (Pub. Health Rep. **42**: 804, 1927); California (Sierra Nevada Mountains), Illinois, and Pennsylvania (Appalachian Mountains), McClendon and Hathaway's map (chart 2); Utah (Rocky Mountains), McClendon (Physiol. Rev. **7**:189, 1927); Wisconsin, Olin; Virginia (Appalachian Mountains), information common to physicians in the state.

by Seidell and Fenger,[28] attributed fundamentally to temperature and weather conditions, and on the reported observations of the greatest incidence of simple goiter at the end of the winter season in some countries and at the end of the rainy season in certain tropical and subtropical countries.

CONCLUSIONS

Reported experimental evidence suggests that a lack of solar radiation may result in a deficiency of the iodine content of the thyroid gland through deficient irradiation of air, soil, food, drinking water or the skin of the organism, and that the mechanism may be a lack of diffusible iodine, an increase in a goitrogenic factor of certain vegetables or a disturbed calcium metabolism.

The relation of solar radiation to the distribution and prevalence of endemic goiter in the United States is suggestive of a relationship of cause and effect which, in the light of present data, would be considered to mean that there tends to result from a deficiency of solar radiation a deficiency of iodine in the thyroid gland due to a lack of solar irradiation of air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of endemic goiter.

II. THE RELATION OF SOLAR RADIATION TO THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN INDIA

In section I, dealing with the same subject as applied to the United States, the evidence was believed to suggest that a deficiency of solar radiation tends to result in an increased prevalence of goiter.

In making a similar comparison for India, the data found to be available for arriving at an index of the distribution of solar radiation differ from those used for the United States. In the United States the relative deficit of solar radiation was determined from the weather bureau reports of the percentage of possible sunshine observed during the winter months. For India the monthly and annual precipitations at different stations have been used in connection with the latitude of the stations. The figures so derived have been compared with computations by Kimball of the depletion of solar rays by water vapor at varying angles of incidence of the sun's rays on the earth's surface. This comparison yields an index of the distribution of solar radiation in India.

Kimball's [27] figures for wavelengths below 346 millimicrons are shown plotted in chart 5. The interpolations are recognized to be liable to considerable error.

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28. Seidell, A., and Fenger, F.: Seasonal Variation in the Iodine Content of the Thyroid Gland, J. Biol. Chem. **13**:517, 1913.

TABLE 1.—*Data for Weather Bureau Stations in India for Calculating an Index of Solar Radiation* *

No.	Station Name	Latitude N		Longitude E	
		Degrees	Minutes	Degrees	Minutes
1	Ahmadabad	23	2	72	38
2	Akyab	20	7	92	57
3	Allahabad	25	28	81	54
4	Bangalore	12	58	77	37
5	Belgaum	15	52	74	30
6	Bombay (Colaba)	18	55	72	54
7	Calcutta (Alipore)	22	32	88	24
8	Cherrapunji	25	16	91	46
9	Cochin	9	58	76	17
10	Gauhati	26	11	91	48
11	Hyderabad	25	23	68	24
12	Jaipur	26	55	75	52
13	Kalat	28	58	66	28
14	Karachi	24	51	67	4
15	Kodaikanal	10	13	77	32
16	Lahore	31	34	74	23
17	Leh	34	10	77	40
18	Madras	13	4	80	15
19	Mandalay	21	59	96	8
20	Mangalore	12	52	74	53
21	Masulipatum	16	9	81	12
22	Mergui	12	27	98	35
23	Moulmein	16	30	96	38
24	Nagpur	21	9	79	9
25	Patna	25	40	85	15
26	Peshawar	34	2	71	37
27	Port Blair	11	41	92	45
28	Quetta	30	12	67	00
29	Rangoon	16	47	96	13
30	Shillong	25	34	91	56
31	Simla	31	6	77	13
32	Waltair (Vizagapatam)	17	42	83	19

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
9	9	76	9	June	27	April, Aug.	0	0	0	0	114	1.48	52	57	33	0.87	19	10
15	10	77	7,688	Oct.	9	April, Aug.	2	16	0	16	62	1.41	59	56	34	0.99	7	8
27	11	92	59	June	18	April, Aug.	0	0	0	0	115	1.515	49	55	35	0.82	24	11
4	12	77	3,021	Sept.	6	April, Aug.	1	8	0	8	35	1.505	50	54	36	1.06	0	0
20	12	74	72	June	38	April, Aug.	0	0	0	0	128	1.442	56	54	36	0.77	29	17
22	12	98	66	July	31	April, Aug.	0	0	0	0	162	1.468	53	54	36	0.68	38	20
18	13	80	22	Nov.	13	April, Aug.	3	24	0	24	49	1.306	69	53	37	1.00	6	12
5	15	74	2,562	July	15	April, Aug.	0	0	0	0	49	1.52	48	51	39	0.96	10	4
21	16	81	15	Oct.	8	May, July	3	24	0	24	39	1.33	67	50	40	0.99	7	12
23	16	96	77	July	45	May, July	0	0	0	0	190	1.42	58	50	40	0.57	49	28
29	16	96	18	July	21	May, July	0	0	0	0	99	1.505	50	50	40	0.78	28	14
32	17	83	38	Oct.	9	May, July	3	24	0	24	41	1.335	67	49	41	0.96	10	13
6	18	72	37	July	24	May, July	0	0	0	0	72	1.494	51	48	42	0.84	22	11
2	20	92	20	July	53	May, July	0	0	0	0	203	1.395	61	46	44	0.48	58	34
19	21	96	250	May	5	May, July	0	0	0	0	35	1.58	42	45	45	0.92	14	3
24	21	79	1,017	July	13	May, July	0	0	0	0	46	1.535	47	45	45	0.87	19	8
7	22	88	21	Aug.	13	May, July	1	8	0	8	64	1.475	53	44	46	0.80	26	14
1	23	72	163	June	11	June	0	0	0	0	28	1.544	46	43	47	0.91	15	5
14	24	67	13	July	2	0	1	8	1	9	7	1.52	48	42	48	1.00	6	2‡
25	25	85	183	Aug.	11	0	2	16	2	18	45	1.386	61	41	49	0.82	24	17
3	25	81	309	July	12	0	1	8	2	10	38	1.458	54	41	49	0.84	22	13
8	25	91	4,309	July	107	0	1	8	2	10	456	1.16	84	41	49	0.12	94	64
11	25	68	96	July	2	0	1	8	2	10	7	1.51	49	41	49	0.97	9	4‡
30	25	91	4,920	June	16	0	0	0	2	2	83	1.505	50	41	49	0.69	37	18
10	26	91	196	July	12	0	1	8	3	11	66	1.44	56	40	50	0.73	33	19
12	26	75	1,431	July	8	0	1	8	3	11	23	1.46	54	40	50	0.88	18	11
13	28	66	6,630	Jan.	1	0	5	40†	5	45	7	1.07	93	38	52	0.92	14	28‡
28	30	67	5,502	March	1	0	3	24†	7	31	9	1.28	72	36	54	0.87	19	20‡
16	31	74	702	July	6	0	1	8	8	16	20	1.42	58	35	55	0.80	26	17
31	31	77	7,232	July	21	0	1	8	8	16	79	1.355	65	35	55	0.58	48	31
17	34	77	11,503	Aug.	1—	0	2	16†	11	27	3	1.334	67	32	58	0.82	24	20‡
26	34	71	7,137	March	2	0	3	24	11	35	13	1.218	78	32	58	0.78	28	28

* The columns as numbered indicate: 1, station number; 2, station latitude; 3, station longitude; 4, station altitude in feet; 5, month of maximum precipitation; 6, precipitation in inches in the month of maximum precipitation; 7, months in which sun is at zenith; 8, months elapsing between last month in which sun is at 90 degrees and month of maximum precipitation; 9, values in column 8 multiplied by 8, the approximate number of degrees per month traveled by the sun (47 degrees in six months); 10, latitudinal distance above 23 degrees 30 minutes; 11, values in column 9 plus values in column 10, giving degrees of declination of the sun from the zenith in the month of maximum precipitation; 12, annual precipitation in inches; 13, index of intensity of solar radiation obtained by plotting columns 6 and 11 into chart 5; 14, index of intensity of solar radiation subtracted from 2 to give an inverse index of solar intensity; 15, minimum angle of the sun (December); 16, sun distant from the zenith in December; 17, index of intensity of solar radiation obtained by plotting columns 12 (annual precipitation in inches) and 16 into chart 5; 18, index of intensity of solar radiation (column 17) subtracted from 106 (maximum index) to give an inverse index of duration or extent of solar intensity; 19, column 14 plus column 18 divided by 2 to give mean of the two methods, precipitation in month of maximum precipitation and degrees of sun's declination from zenith in month of maximum precipitation, and annual precipitation and sun's declination from zenith in December, respectively: minus 25 (minimum index thus obtained) to give zero as minimum index.

† As the angle of declination of the sun is great in the month of maximum precipitation, with only slight precipitation (less than 10 inches per annum), an exaggerated value is doubtless given to the value in column 14, and thus to the value in column 19.

‡ Annual precipitation less than 10 inches.

Table 1 shows certain data reported from weather bureau stations in India;[29] the annual and monthly precipitation for each station; the angle of the sun's rays at each station in the month of maximum precipitation and in December, the angle being measured in terms of degrees distant from the zenith. These data as to the angle of the sun's rays and precipitation, plotted into chart 5, afford a numerical index of solar radiation according to Kimball's computations.[30] The comparison furnishes an index only rather than a measurement, as precipitation in inches is substituted for Kimball's value of water vapor per centimeter. In the last column of table 1, the index is transcribed into a

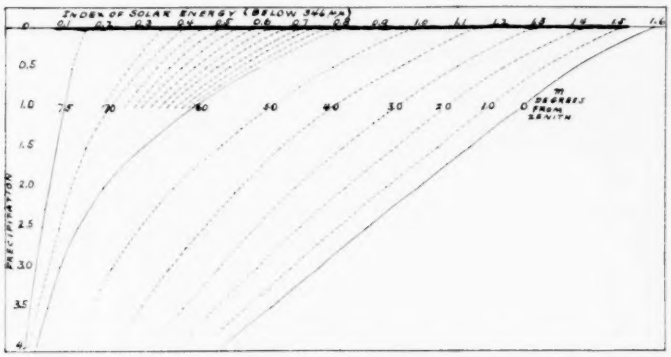

Chart 5.—Energy distribution in solar rays below 346$\mu\mu$, as modified by air mass and water vapor. m represents air mass; m equal to 0, solar energy outside the atmosphere; m equal to 0.764, for Calama, Chile, sun in zenith, atmospheric pressure averages 58.1 cm.; m equal to 1, for Washington, D. C., sun in zenith; m equal to 2, for Washington, D. C., solar zenith distance, 60 degrees; m equal to 4, for Washington, D. C., solar zenith distance, 75 degrees 7 minutes. (After Kimball.)

29. Clayton, H. H.: World Weather Records, Pub. 2913, Washington, D. C., Smithsonian Institution, 1927.

30. It is not intended to assume a special influence for the wavelengths used from Kimball's table, though to the shorter lengths of solar radiation is generally ascribed a biologic influence greater than to the longer wavelengths. The radiation index arrived at by plotting the declination from 90 degrees of the sun's angle in the month of maximum precipitation and the precipitation in this month is conceived of as an index of intensity of depletion of solar rays, whereas the radiation index arrived at by plotting the declination in December and the annual precipitation is conceived of as an index of duration or extent of depletion of solar rays. There is no certainty of the validity of either assumption. Probably the whole method of computing a radiation index is needlessly complex, and if simplified it would be to the advantage of clarity at least. Figures for cloudiness at the different stations, similar to those employed in the paper on conditions in the United States, might be useful if available. Precipitation is not an accurate index of either cloudiness or humidity.

reversed scale. In this form the index is shown on the maps of distribution of goiter as prepared by McCarrison [31] (chart 6), and by Megaw [32] (chart 7), as also on the map of distribution of deaf-mutism as prepared by Stott and his co-workers [33] (chart 8). The last comparison has the advantage that deaf-mutism is noted in the census of India and

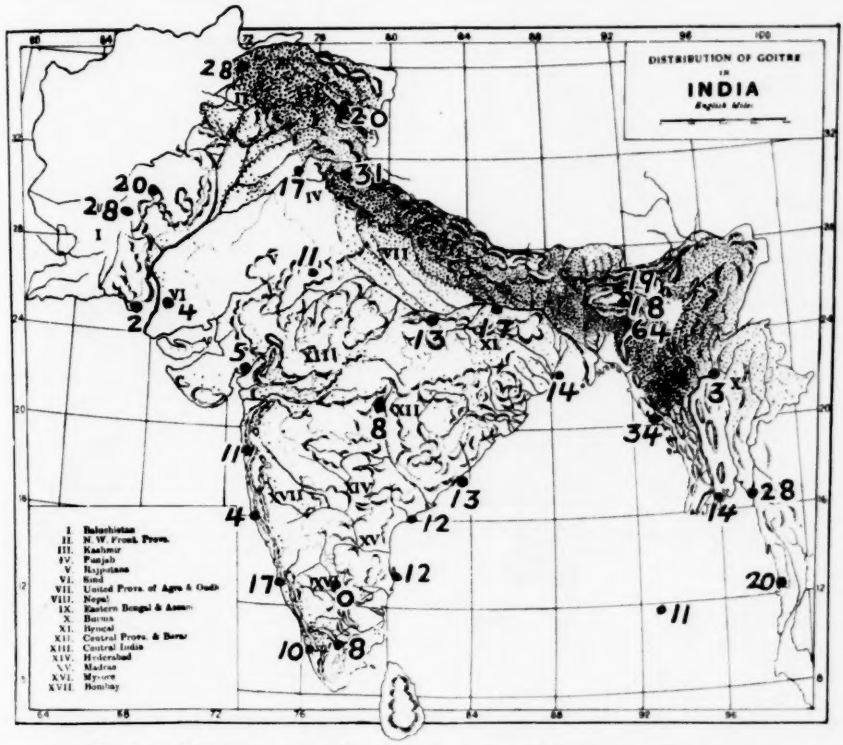

Chart 6.—Distribution of goiter in India (after McCarrison). The numerals indicate the radiation index (depletion) at thirty-two weather bureau stations.

the figures are given per unit of population; it has the disadvantage that it substitutes an index of goiter (deaf-mutism) for the disease

31. McCarrison, R.: The Distribution of Goitre in India, Indian J. M. Research **2**:778, 1914-1915.

32. Megaw, J. W. D., and Gupta, J. C.: The Geographical Distribution of Some of the Diseases of India, Indian M. Gaz. **62**:299, 1927.

33. Stott, H.; Bhatia, B. B.; Lal, R. S., and Rai, K. C.: The Distribution and Cause of Endemic Goiter in the United Provinces, Indian J. M. Research **18**:1059 (April) 1931.

itself. The basis on which Stott and his co-workers claimed the validity of the substitution is as follows:

> The close connection between deaf-mutes, cretins and goiter is well known, but since the census records the distribution of deaf-mutes in each province of India, and since these figures are utilized later as an indication of the distribution of goiter in India, it is desirable to produce definite evidence of this close connection.

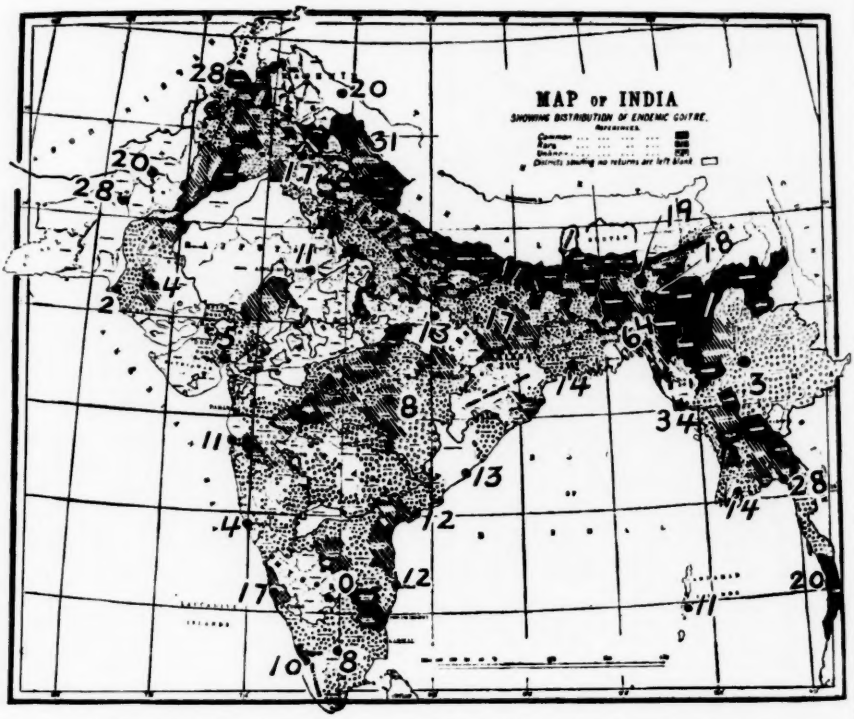

Chart 7.—Distribution of endemic goiter in India (after Megaw and others). The shading indicates the presence of goiter: black, common; hatched, rare; small circles, goiter unknown; blank spaces, districts sending no returns. The numerals indicate the radiation index (depletion) at thirty-two weather bureau stations.

In the United Province census report for 1901, the following figures are given for the Gonda Tahsils:

	Goiter Cases Attending Dispensaries			
Tahsil	Total Number	per 10,000 Population	or as	Deaf-mutes per 10,000
1. Gonda	19,385	509	5.6	4.7
2. Tarabganj	29,971	821	9.1	9.3
3. Utraula	5,899	90	1.0	2.7

Allowing for the large percentage of non-goitrous Nepalese who come to the Utraula dispensary with ordinary complaints, the tahsil ratio for goiter and for deaf-mutes is practically identical. This is interesting evidence. But similar figures could be presented for any sufficiently endemic area in the U. P., for goiter, cretinism and deaf-mutes everywhere occupy the same areas of the highest endemicity. . . . In India, therefore, the distribution of deaf-mutes may be taken as an index of the distribution of severely affected endemic goiter areas.

The correlations shown on the three maps (charts 6, 7 and 8) between the relative deficiency of solar radiation and the presence of

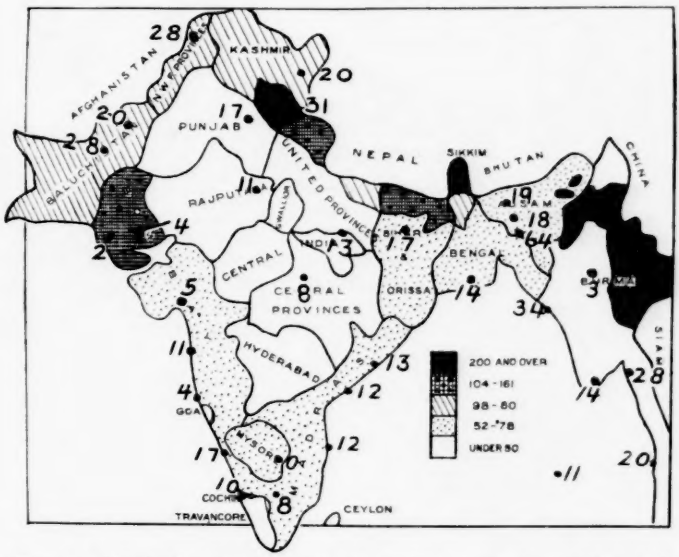

Chart 8.—Distribution of deaf-mutes per hundred thousand population in India (after Stott and others). The significance of the shading is shown in the chart. The numerals indicate the radiation index (depletion) at thirty-two weather bureau stations.

goiter and deaf-mutism, respectively, appear to be fairly close except for the sub-Himalayan area along the northern border of India. The exception appears to be due to the fact that there are no reports of precipitation from any station located north of the Ganges River, where the prevalence of goiter is relatively great. That precipitation in this area is also great in comparison with the area south of the Ganges is shown by reference to charts 9 and 10. The area is at a relatively great distance from the equator, and is subject, therefore, to a relatively great depletion of solar radiation by air mass. In this connection the follow-

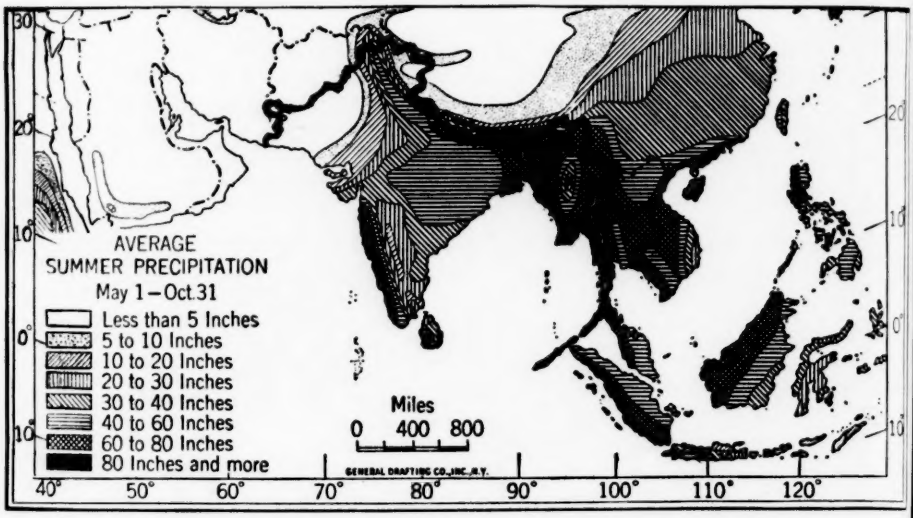

Chart 9.—Average summer precipitation in India, from May 1 to October 31 (reproduced from Barrows, H. H.; Parker, E. P., and Parker, M. T.: Geography, Europe and Asia, New York, Silver, Burdett and Company, 1927, where the chart was reproduced from Philips' Modern School Atlas (by permission of Messrs. George Philip and Son, Ldt., London). The borders of India drawn in black in the present reproduction are not to be confused with the black areas representing precipitation of 80 inches and more, as in Burma, where the boundary line appears in white.

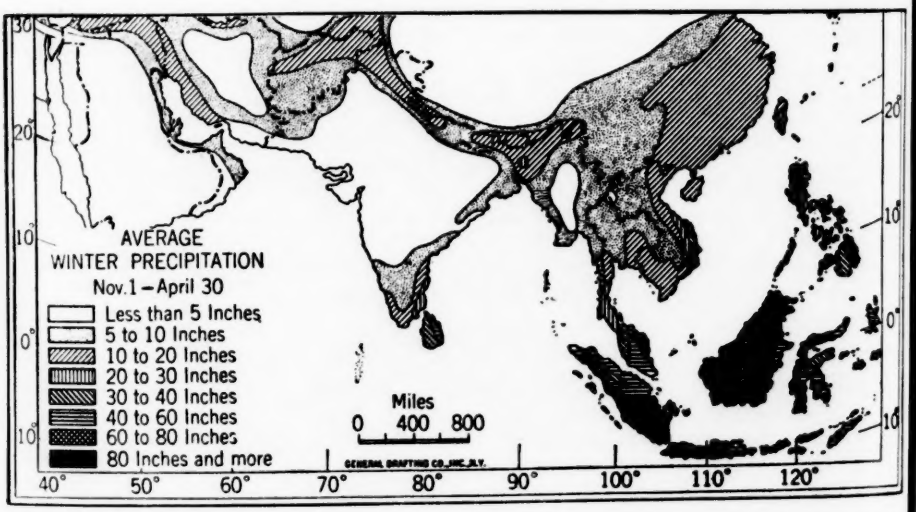

Chart 10.—Average winter precipitation in India, from November 1 to April 30 (reproduced from the same sources as chart 9).

ing quotation from the Encyclopaedia Britannica (eleventh edition) appears to be significant:

> India: flora—For the Malayan area, which Sir Joseph Hooker describes as forming "the bulk of the flora of the perennially humid regions of India, as of the whole Malayan peninsula, Upper Assam Valley, the Khasi mountains, the forests of the base of the Himalaya from the Bramaputra to Nepal, of the Malabar coast, and of Ceylon" . . . indicative of the character of the climate of the sub-Himalayan area.

The sub-Himalayan tract is, therefore, apparently subject to solar radiation of a degree comparable with that of Simla (latitude 31° 6′, longitude 77° 13′, radiation index 31).

The foregoing considerations appear to furnish suggestive evidence of a direct relation between a deficit of sunshine and the presence of endemic goiter in India similar to the broad scale study of the same correlation in the United States.[34]

McCarrison's [31] discussion of distribution with respect to rainfall is as follows:

> Speaking generally there appears to be little connexion between the rainfall and the prevalence of goitre. The disease is as common in some parts of India where the rainfall is scanty as in others where it is very high. I have, however, received many reports in which it is stated that goitre most commonly commences and most rapidly develops during or after the rains. So constant is this belief, first recorded by Macnamara [35] thirty years ago, that I am inclined to attach considerable importance to it, and to attribute to "the rains" an etiological influence which depends rather upon factors associated with them—inundation, contamination of drinking water-supplies by surface washings, etc.—than upon the rainfall itself.

The paper of Stott and his co-workers gives opportunity for more detailed comparison of climatic conditions and the distribution of goiter. These authors interpret their observations as pointing to the influence of lime in the causation of goiter, and in support of their thesis cite extensive evidence both general and specific. Their position may be represented by the following quotation from their summary:

> Where the local distribution of this disease group (congenital deaf-mutes, cretins and goitrous persons) has been investigated it is associated with a definite water-supply and in that water-supply lime is usually found present in excessive amounts.

---

34. It is of interest to note that the lowest radiation index, zero, is at Bangalore (latitude 12° 58′ N, longitude 77° 37′ E, altitude 3,021 feet), nearly the location of Coonoor (latitude 11° 21′ N, longitude 76° 49′ E, altitude about 6,000 feet [National Geographic Society]), where goiter is reported to be notable for its rarity. McCarrison (Indian J. M. Research **18**:1311, 1931) stated: "It should here be emphasized that three conditions in Coonoor—altitude, calcium content of the soil and iodine content of the soil and vegetables grown upon it—all have an influence on the thyroid gland. The height of Coonoor above sea level is 6,000 ft., the soil is very poor in calcium, and relatively rich in iodine."

35. Macnamara, F. N.: Climate and Medical Topography in Their Relation to the Disease-Distribution of the Himalayan and Sub-Himalayan Districts of British India, London, Longman [and others], 1880.

The interpretation by these authors of their several references to climate is perhaps indicated by the following quotation:

> South of the Gogra (river), in the dry sandy areas of Fyzabad, there is no goiter, because the Gogra tributaries which keep the soil moist and calcium-saturated all flow from the north.

There appears to be no inherent conflict between the view of these authors and that of a more direct influence of deficiency of solar rays as affecting the air, soil, food, drinking water or the skin of the animal organism of the population concerned. Regardless of interpretation, it

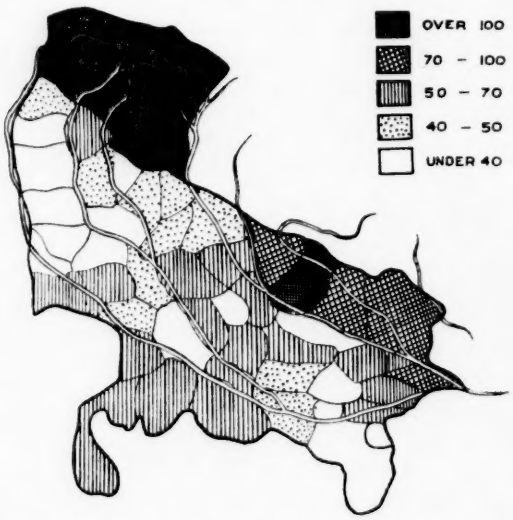

Chart 11.—Distribution of deaf-mutes in the United Provinces of India, per hundred thousand males; Census, 1921. (After Stott and his co-workers.)

seems pertinent to reproduce maps 5, 6 and 8 of Stott and his co-workers as charts 11, 12 and 13 of this series, together with certain extracts from the paper of these authors referring to climatic conditions.

Charts 11 and 12, and especially chart 13, permit a comparison of the goiter-free area of Fyzabad and Barabanki with the heavily goitrous districts of Bahraich, Gonda, Basti and Gorakhpur just north of the Gogra River. The dry character of Fyzabad has been referred to. The sub-Himalayan tract of the United Provinces, lying just north of the Gogra, is shown with the distribution of goiter in chart 13, as also its division into three transversely parallel tracts. The characteristics of these three natural subdivisions as given by the authors quoted are as follows:

(1) The foothill (Terai) tract.

(2) The plateau (Uparhar) tract.

(3) The low-lying moist (Tarhar) tract.

The latter is an endemic area of high degree. The former two areas will also be considered in this section.

The sub-mountainous foot-hill (Terai) tract lies between the Himalayas to the north and the river Rapti to the south. The area is full of small mullahs, dry in the hot weather but which serve to draw off mountain water in the rains and which then form many swamps. To the extreme north there is a line of forest

Chart 12.—Key map to the districts and rivers of the United Provinces of India. (After Stott and his co-workers.)

land (as jungle is cleared and water supplies are improved the disease decreases) where the heavy clay forming the soil of this region gives way to sandy clay which is interspersed with water-worn limestone boulders and lime kanker from the mountains. . . . Along the Rapti river the villages are goitre free, nor does the disease become intense until about one mile from the forest border is reached, where the villages commence to show an increasing prevalence from 3-5 per cent. The worst villages, some of which show a rate of 30 per cent, are situated on the edge of the rivulets. The disease in general is not severe here.

The plateau (Uparhar) tract is separated from the foot-hill tract on the north by the river Rapti, and from the low-lying moist Tarhar tract to the south by the rivers Sarju, Tehri and Kuwano. The tract is a slightly raised plateau. The soil

is a stiff clay, unsuited to maize but the grain harvests are rich and the Uparhar is the most flourishing part of each district. Wells are plentiful. The tract is almost free from endemic goitre.

In the low marshy (Tarhar) tract . . . the climate is naturally humid . . . the tract shows intensely endemic areas where the tributaries from the Himalayas join the Gogra. The most endemic of all areas is that lying between the three rivers Tehri, Sarju and Gogra where the goitre rate is 70 per cent and which is known as "the home of fools." The soil of these areas is intensely damp and the subsoil water is at a high level, especially during the rains. Like that of the Padrauma Tahsil the soil is alluvial, friable and porus with 9 per cent calcium. . . . The climate is very moist, the rainfall (50-70 inches) being higher than in any other plain district of the province.

Chart 13.—The distribution of goiter in the Bahraich, Gonda, Basti and Gorakhpur districts of the United Provinces, India. (After Stott and his co-workers). The shading indicates: gray, 5 per cent; hatched, from 10 to 25 per cent; small dots, from 25 to 35 per cent; small circles, from 35 to 50 per cent, and black, from 50 to 70 per cent.

In the Himalayan tract (of the United Provinces) . . . unlike the plains where endemic goitre is found in large areas, in the hills goitre is scattered in different and often not adjacent villages. These endemic villages are situated in the moist river valleys. . . . Villages over 5000 feet in cool climates appear free. . . .

In no waters, goitrous or otherwise in the U. P. was iodine noted.

The foregoing references to the distribution of goiter could be supplemented by references to the distribution and prevalence of deaf-mutism in connection with climatic conditions involving the depletion of solar radiation. The quotations that have been made appear to take on

special significance in view of the following observations by Stott and his collaborators:

> Season: New goitres especially arise, old goitres enlarge and all goitres most rapidly develop during and after the rains, i. e., during October, November and December. For it is during the monsoon in the plain areas that the rivers overflow their banks and alluvium with the goitre producing substance in it is spread over the soil and readily reaches the shallow wells. Attendance of out-patients at the various dispensaries for goitre increases largely during the months following the rains.

Chart 14, reproduced from the paper of Stott and his co-workers, shows this tendency to increase in attendance at the dispensary of the

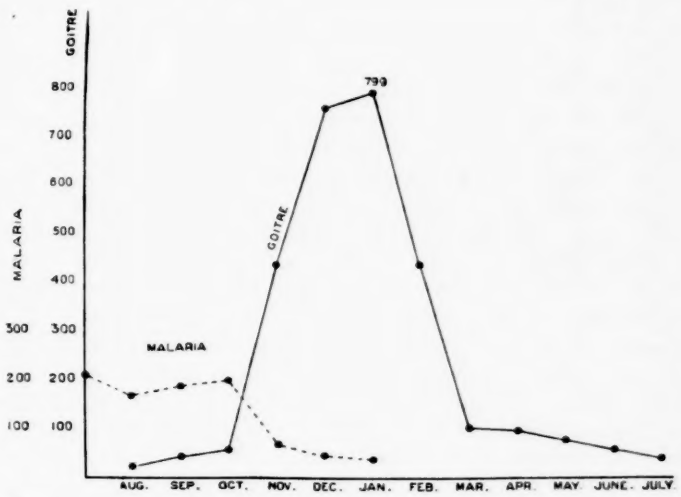

Chart 14.—The monthly goiter (and malarial) attendance at the Banpur Hospital, 1925-1926. (After Stott and his co-workers.)

Banpur Hospital (latitude 19° 47′ N, longitude 85° 10′ E [36]) in the months following the rains. This location on the east coast is about midway between Calcutta on the north and east and Waltair on the south and west, and the monthly distribution of rainfall at these two stations is as follows: [29]

	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Year
Calcutta:	0.42	0.99	1.38	2.18	5.56	11.91	12.70	13.38	10.01	4.90	0.65	0.24	64.32
Waltair:	0.36	0.48	0.33	0.71	2.31	4.56	4.68	5.75	7.21	9.36	4.10	1.21	41.05

36. National Geographic Society, Washington, D. C., personal communication.

CONCLUSION

The data in this section appear to support the conclusions in the first section dealing with endemic goiter in the United States; namely, that a deficiency in solar radiation tends to a deficiency of the iodine content of the thyroid gland due to a lack of irradiation of the air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of endemic goiter.

III. THE RELATION OF SOLAR RADIATION TO IODINE OF THE SOIL AND THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN NEW ZEALAND

In section I, dealing with the relation of solar radiation to the distribution and prevalence of endemic goiter in the United States, the evidence was believed to suggest that a deficiency of solar radiation tends to an increased prevalence of goiter.

In section II, examination of the data for India seemed to point to the same conclusion. The index of solar radiation used in the two sections was different on account of differences in the data available. For the United States solar radiation was expressed in terms of percentage of possible sunshine; for India the index was the depletion of certain rays of the sun by water vapor at varying angles of incidence of the sun's rays on the earth's surface. The relative depletion at the different weather bureau stations in India was arrived at by taking into account the sun's angle and the precipitation. A scale of precipitation in inches was substituted for the measurement of water vapor in centimeters if all the water vapor of the air were precipitated, as described in Kimball's [27] article. With this substitution, an index of depletion of solar radiation was calculated by comparison with Kimball's standards.

In this section data reported by Hercus, Benson and Carter [37] permit a consideration of solar radiation in relation to iodine of the soil of New Zealand in addition to the relationship discussed in the two preceding sections. In this section the index of solar radiation is the same as that described for India with the following differences. The precipitation and the sun's angle during the month of lowest incidence of the sun's rays (June in New Zealand), compared with Kimball's standards, is used as the index of radiation. Since the actual monthly precipitation in June was not available for all the districts of New Zealand under consideration, this factor was estimated by taking the annual precipitation for the district as given in the article of Hercus, Benson and Carter and applying to this annual rainfall the relative

37. Hercus, C. E.; Benson, W. N., and Carter, C. L.: Endemic Goitre in New Zealand, and Its Relation to the Soil-Iodine, J. Hyg. **24**:321, 1925.

amount in June as suggested by the reported June precipitation at four weather bureau stations in New Zealand in "World Weather Records," [29] assuming for each district in New Zealand a monthly distribution of rainfall corresponding to that at the nearest station for which the data

TABE 2.—*Data Relative to Solar Radiation of New Zealand Districts* *

1	2		3		4		5	6	7	8
	Degrees	Minutes	Degrees	Minutes	Degrees	Minutes				
1	47		19	30	70	30	H	60	5.00	0.285
2	46	30	20		70		H	45	3.73	0.325
3	46		20	30	69	30	H	40	3.32	0.352
4	46		20	30	69	30	C	35	3.67	0.340
5	45	30	21		69		C	22	2.31	0.394
6	45	30	21		69		C	22	2.31	0.394
7	46		20	30	69	30	C	37	3.88	0.340
8	45		21	30	68	30	C	20	2.10	0.412
9	44		22	30	67	30	C	70†	7.35	0.338
10	43	30	23		67		C	70†	7.35	0.350
11	43	30	23		67		C	40	4.20	0.420
12	43		23	30	66	30	C	70†	7.35	0.364
13	42		24	30	65	30	C	26	2.73	0.505
14	41	30	25		65		W	50	5.00	0.460
15	42		24	30	65	30	H	100	8.30	0.368
16	41	15	25	15	64	45	W	60	6.00	0.440
17	41	15	25	15	64	45	W	60	6.00	0.440
18	41		25	30	64	30	W	40	4.00	0.504
19	39	30	27		63		W	40	4.00	0.550
20	38	30	28		62		A	50	5.50	0.523
21	40	30	26		64		W	40	4.00	0.518
22	40	15	26	15	63	45	W	40	4.00	0.525
23	39	45	26	45	63	15	W	40	4.00	0.540
24	39		27	30	62	30	W	65	6.50	0.482
25	39	30	27		63		W	70	7.00	0.457
26	39		27	30	62	30	A	60	6.60	0.478
27	38	15	28	15	61	45	A	60	6.60	0.497
28	38		28	30	61	30	A	60	6.60	0.501
29	38	30	28		62		A	60	6.60	0.490
30	38	30	28		62		A	60	6.60	0.490
31	37		29	30	60	30	A	75	8.25	0.470
32	36	30	30		60		A	42	4.62	0.610
33	35	30	31		59		A	60	6.60	0.560

* The columns as numbered indicate: 1, district number; 2, approximate latitude; 3, minimal seasonal angle of sun (June); 4, distance from zenith of angle of sun in June; 5, weather bureau station from which figures are taken for ratio of June precipitation to annual precipitation: A, Auckland; C, Christchurch; H, Hokitika; W, Wellington; 6, annual precipitation in inches; 7, calculated June precipitation; 8, radiation index derived from plotting distance from zenith of angle of sun in June (column 4) and calculated June precipitation (column 7) in chart 5.

In column 5, Hokitika was selected as the standard for the ratios in districts 1, 2 and 3 because of the statement in the Encyclopaedia Britannica (fourteenth edition) that, at Invercargill, like Hokitika, spring is often wettest, rather than like Dunedin and Lincoln near Christchurch, where the total rainfall is generally distributed through the year. However, the distinctions are not great, as shown by the following ratios of June precipitation to annual precipitation: Auckland, 11 per cent; Christchurch, 10.5 per cent; Hokitika, 8.3 per cent; Wellington, 10 per cent.

† According to Hercus, Benson and Carter, the rainfall in district 9, South Canterbury, varies considerably in different parts of the district. The inference from their comments on district 10, Christchurch, and district 12, North Canterbury, is that there is a similar variation in these districts. The figure 70 used in the table to represent the annual rainfall in each of these three districts is the mean of the figures given by Hercus, Benson and Carter for the area of greatest rainfall (40 to 100 inches), as the high incidence of goiter in these districts suggests that for purposes of correlation the greatest permissible value be assigned to supposed goiter-producing factors. However, the procedure involves statistical practice that is open to criticism.

were thus available. It is, of course, evident that, with these several substitutions, no actual measurement of depletion has been arrived at, and that as an index the estimate is only approximate at best. This value is referred to as the radiation index, and will be applied to each of the districts of New Zealand described by Hercus, Benson and Carter (charts 15 and 16). The data are summarized in table 2.

Hercus, Benson and Carter regarded their investigation of the amount of iodine in the soil as a study of the "soil of plant food, and therefore, indirectly, of human food." They concluded that "the hypothesis that goitre is caused by a deficiency of iodine in the diet has been fully sustained by the present investigation." They stated further: "Reasons have been deduced also for believing that a relation holds between the incidence of goiter and the distribution of geological formations (as determining the nature of the soil) in New Zealand,

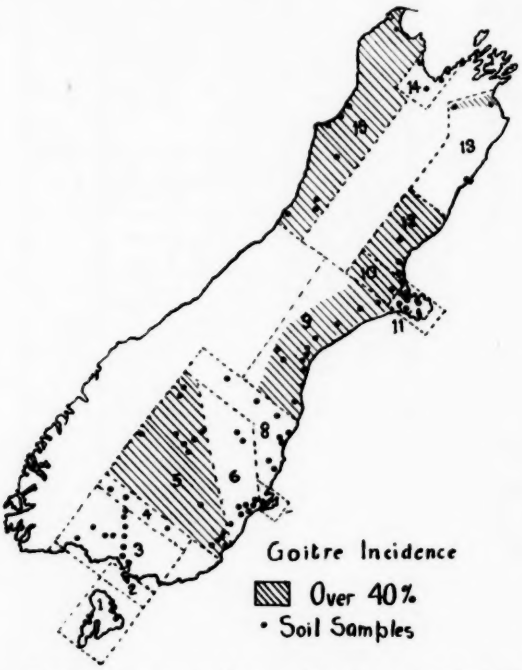

Chart 15.—Districts of goiter incidence and localities of analyzed soils in New Zealand, South Island. (After Hercus, Benson and Carter.)

Switzerland, and perhaps in other countries." As supplementary to their study, in the present article consideration will be given to a possible influence of solar radiation on the iodine content of the soil and on the incidence of endemic goiter in New Zealand.

Chart 17 reproduces the curves of Hercus and his co-workers, showing the relationship between the average amount of iodine in the soils and the regional incidence of goiter among school children and military recruits in New Zealand. Only the former group is considered

in this article. The curve is according to the formula $y = \frac{360}{x} + 6$ when y equals goiter and x equals iodine.[37]

For reference charts 15, 16, 18 and 19, from Hercus, Benson and Carter, are reproduced.

The geological data shown in these maps are more particularly detailed in a table prepared by Hercus, Benson and Carter of the amount of iodine in New Zealand soils of different origin and nature. Their description of the classification of the different soils is as follows:

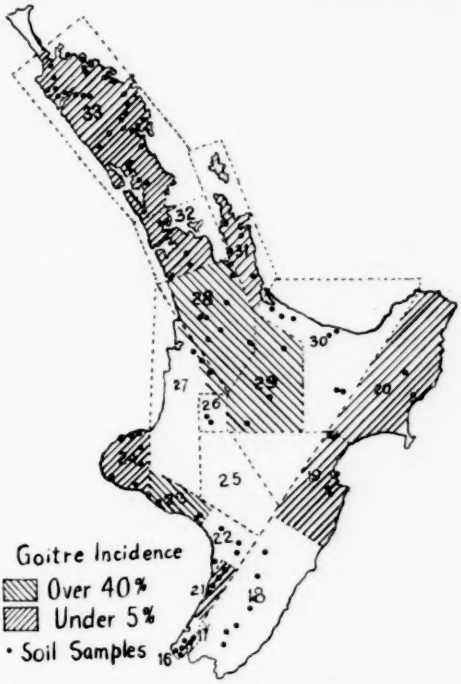

Chart 16.—Districts of goiter incidence and localities of analyzed soils in New Zealand, North Island. (After Hercus, Benson and Carter.)

The main types of geological formations are indicated by the Roman numerals I to VI with suffixes according to the special variety indicated:

I indicates plutonic rocks (which are not very widespread). Ig and In stand for the acid siliceous granites and basic norites respectively.

II indicates mica schist, a much more widespread formation in the South Island.

III indicates greywackes, argillites, etc., which form most of the highlands in New Zealand. (They are mostly rocks of Mesozoic, but also in part of Paleozoic age.) The mica schists were derived by metamorphism from rocks similar to these.

IV indicates the younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke. They are very varied, including conglomerates and

sandstones (sometimes with coal measures) (s), greensands (gs), claystone or marl (c), limestone (l), and volcanic tuffs (t) and are indicated respectively by IVs, IVgs, IVc, IVl, IVt.

V indicates volcanic rocks which are either acid (rhyolite, rhyolite tuff and pumice or siliceous dacites), intermediate (andesite) or basic (basaltic). These are indicated by the signs Va, Vm, and Vb respectively. Phonolites are comparatively rare and are indicated by Vp.

VI indicates a widespread and varied group of post-Tertiary sediments of fluvatile, marine, or glacial origin. They are classified thus:

VIg (gravel), VIs (silts—mixed mud and sand).

VIsa (sands in beach or river), VIsw (swamp deposits).

VIds (dune sands), VIls (loess deposits), VIc (clays).

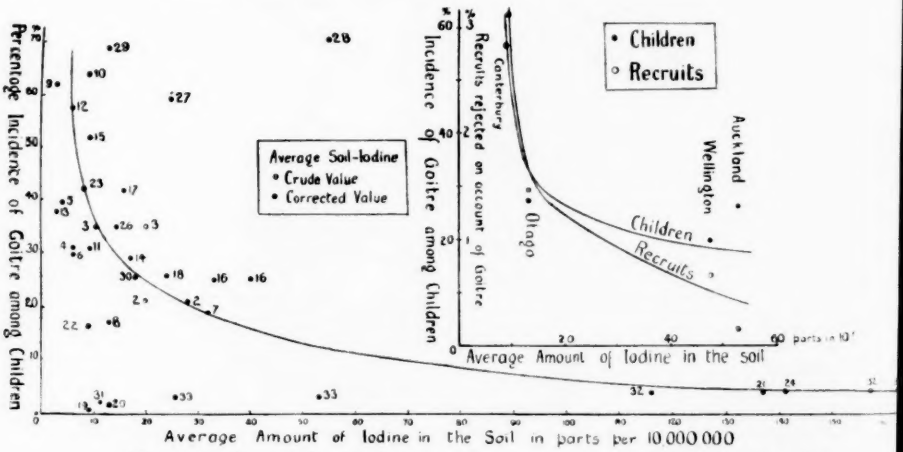

Chart 17.—The relationship between the average amount of iodine in the soils and the regional incidence of goiter among school children and military recruits in New Zealand. The figures by dots denote the districts indicated in table 2. (After Hercus, Benson and Carter.)

Where it is of importance to indicate the formations immediately underlying the post-Tertiary cover this is done by writing the symbol for the upper formation above that of the lower, as the numerator and denominator in a fraction.

From the weathering of these formations, various types of soil are derived, the natures of which are indicated by the symbols in the second column of the table. The colour of the soil is indicated by capital letters: B, black; Br, brown; R, red, G, gray; W, white; and Y, yellow; while the texture of the soil is indicated by small letters: clayey (c), gritty (g), loamy (l), micaceous (m), sandy (sa), silty (s), stony (st), and where peaty or full of plant remains (v).

That portion of Hercus, Benson and Carter's paper relating to the various types of soils derived from the weathering of the geological formations has not been taken into consideration here. The rest of the data in their table have been redistributed in table 3 so as to show

the different districts represented by soil of a given type and the number of samples from each district. In this way it is possible to compare the iodine content of samples of a given geological formation with other data related to the different districts.

In charts 20 to 28 a comparison has been made between the radiation index determined as described in the earlier part of this section

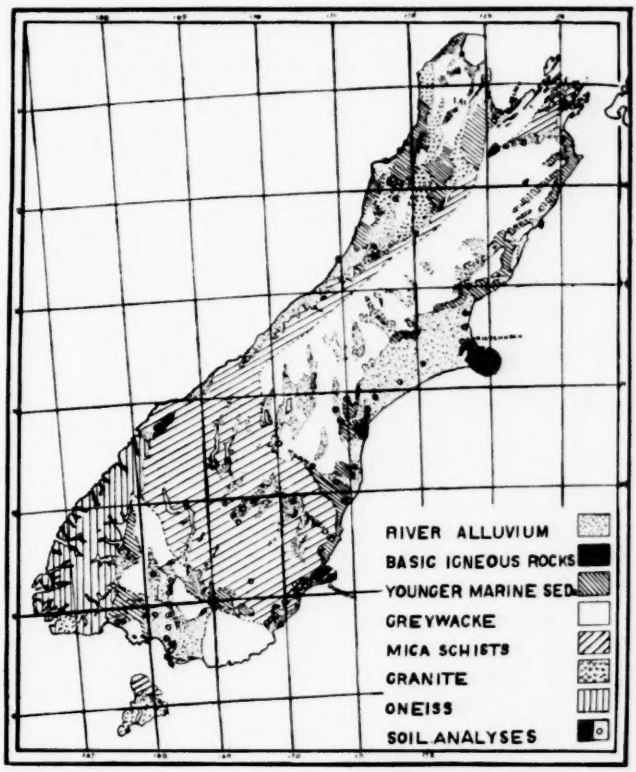

Chart 18.—Geological sketch-map of New Zealand, South Island. (After Hercus, Benson and Carter.)

and the iodine content of the soil of a given geological formation. In some instances the districts represented by a given geological formation are too few to make a comparison profitable, and these have not been plotted. In chart 29 a comparison is made between the radiation index and the average iodine content of the soil of each district.

TABLE 3.—*Amount of Iodine (Parts per 10^7) in New Zealand Soils of Different Origin and Nature. (After Hercus, Benson and Carter)* *

	Ig	VI / Ig	In	II	VI / II	III	VI / III	IV	VI / IV	Vb	VI / Vb	Vm	VI / Vm	Va	Vp	VI: g	gs	s	sa	sw	ds	ls	e	l
1	127 (2)	...	...	6 (1)	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
2	...	...	20 (3)	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
3	...	...	...	...	...	...	...	10.8 (5)	...	...	...	...	...	...	...	...	...	23.3 (24)	...	3 (2)	...	...	...	...
4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	6.3 (6)	...	...	...	...	...	...
5	...	...	...	2.7 (16)	3.3 (30)	9.5 (2)	10 (2)	6.5 (8)	...	...	...	...	...	...	...	...	...	3.4 (7)	...	...	...	...	...	...
6	...	...	...	7 (1)	5 (3)	...	...	0.0 (1)	...	5 (2)	...	...	...	...	...	...	...	6.5 (17)	14 (1)	...	...	...	...	...
7	...	...	...	...	...	...	...	...	18 (3)	21.3 (19)	10.6 (3)	14.6 (10)	18 (1)	...	25 (1)	...	...	...	...	62.3 (19)	2 (1)	...	15 (3)	...
8	...	...	...	...	...	2 (1)	...	18.6 (10)	...	29 (2)	...	...	...	...	...	8.6 (5)	...	5.7 (7)	...	...	...	...	...	7 (2)
9	...	...	...	...	...	...	...	...	3.6 (3)	...	4 (2)	...	...	...	...	0.0 (1)	...	3 (8)	...	...	...	...	...	...
10	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	10.6 (16)	1 (2)	...	0 (1)	...	...	...
11	...	...	...	...	...	...	...	...	...	...	8.7 (8)	...	...	...	...	...	...	...	...	...	...	...	...	...
12	...	...	...	...	...	...	...	...	6 (1)	...	...	...	...	...	...	...	...	5.3 (2)	...	...	...	...	...	...
13	...	...	...	...	...	...	...	0.0 (1)	...	...	...	...	...	...	...	...	...	5 (2)	...	2 (1)	...	...	...	...
14	4 (1)	...	...	...	...	11 (2)	...	38 (1)	...	38 (1)	...	...	...	...	...	10 (2)	10.5 (4)	...	...	42 (1)	...	...	...	...
15	...	48 (1)	...	...	...	...	...	...	...	...	...	...	...	...	...	2.3 (4)	...	12.7 (4)	...	...	...	...	...	...
16	...	...	...	...	...	36.5 (8)	34 (2)	...	...	...	...	...	...	...	...	...	...	...	...	78 (2)	...	...	...	...
17	...	...	...	...	...	...	16 (2)	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
18	...	...	...	...	...	...	...	25 (4)	47 (2)	...	...	...	...	...	...	...	...	6.6 (3)	...	...	...	...	...	...

| | | |

regardless of geological formation, according to the iodine content value used by Hercus, Benson and Carter in their paper.[38]

In charts 30 to 40 a comparison is made between the radiation index and the incidence of endemic goiter, the districts being grouped in each chart so as to make the chart represent a single geological

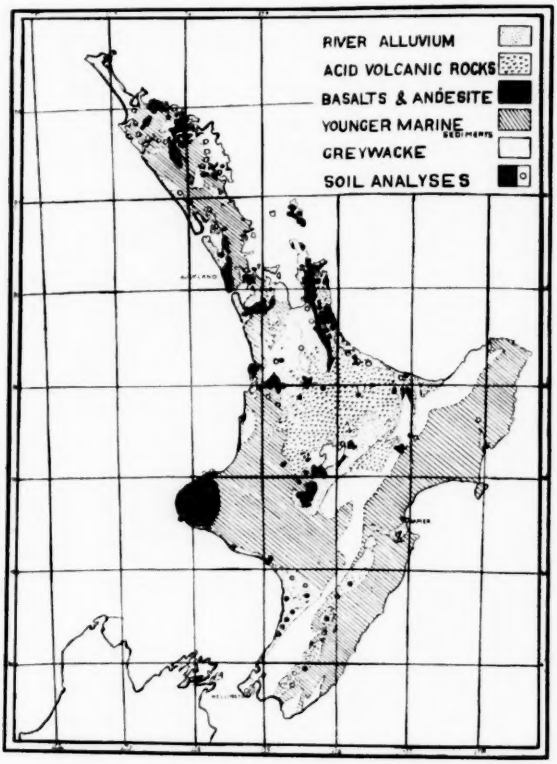

Chart 19.—Geological sketch-map of New Zealand, North Island. (After Hercus, Benson and Carter.)

formation. In chart 41 a comparison is made between the radiation index and the incidence of endemic goiter in each district, regardless of geological formation.

38. In a few instances these authors used a corrected value obtained by omitting from the calculation of the average abnormally large figures that they considered could not be taken as fairly representative of considerable areas of agricultural or pastoral land.

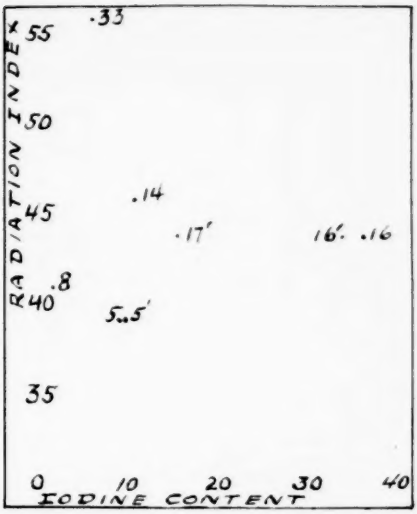

Chart 20.—The relation of the radiation index to the amount of iodine in the soils of geological formations III (greywackes, argillites, etc., mostly rocks of Mesozoic but also in part of Paleozoic age) and $\frac{VI}{III}$ (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ′ by figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

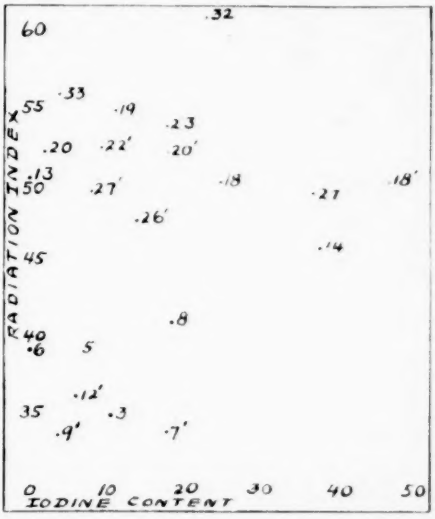

Chart 21.—The relation of the radiation index to the amount of iodine in the soils of geological formations IV (younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke) and $\frac{VI}{IV}$ (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ′ by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

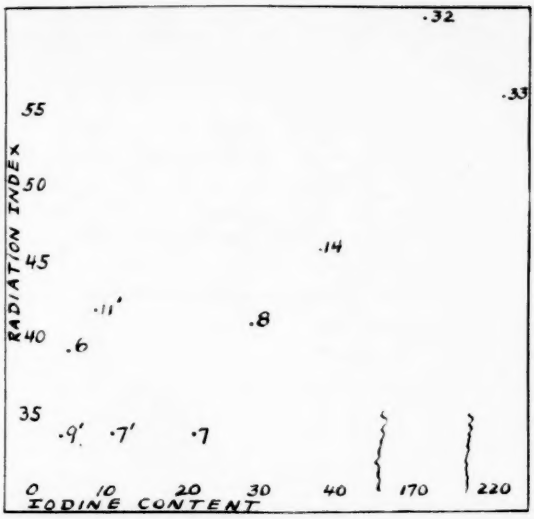

Chart 22.—The relation of the radiation index to the amount of iodine in the soils of geological formations Vb (volcanic rocks which are basic-basaltic) and $\frac{VI}{Vb}$ (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ' by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

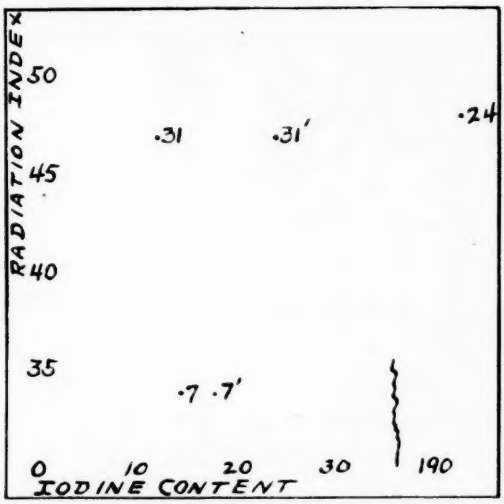

Chart 23.—The relation of the radiation index to the amount of iodine in the soils of geological formations Vm (volcanic rocks which are intermediate—andesite) and $\frac{VI}{Vm}$ (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ' by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

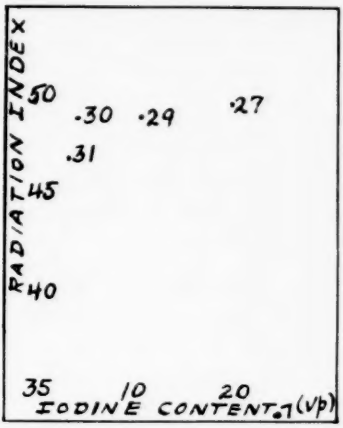

Chart 24.—The relation of the radiation index to the amount of iodine in the soils of geological formation Va (volcanic rocks that are acid-rhyolite, rhyolite tuff and pumice or siliceous dacites), according to Hercus, Benson and Carter. The figures by dots denote districts.

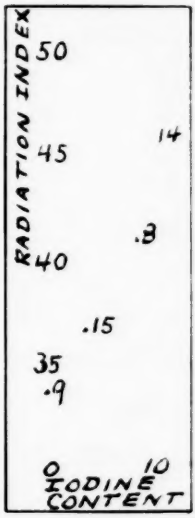

Chart 25.—The relation of the radiation index to the amount of iodine in the soils of geological formation VIg (gravel from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

Examination of charts 20 to 41 appears to warrant the notations in table 4.

Generalizing from table 4, it may be said with reference to the geological formations from which relatively large numbers of samples were examined that there is seen some tendency to correlation between

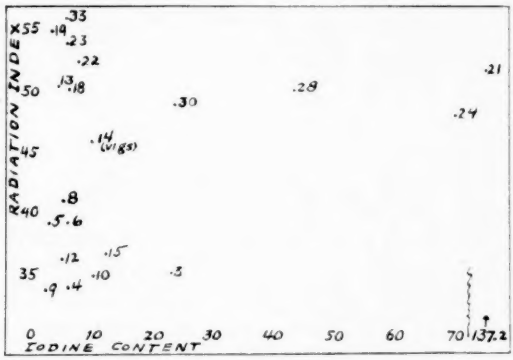

Chart 26.—The relation of the radiation index to the amount of iodine in the soils of geological formation VIs (silts—mixed mud and sand—from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

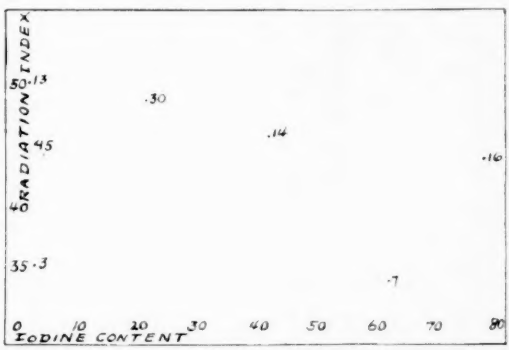

Chart 27.—The relation of the radiation index to the amount of iodine in the soils of geological formation VIsw (swamp deposits from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

the radiation index and the iodine content of the soil of a given geological formation, and also between the radiation index and the iodine content of the soil of all the different geological formations taken as a

group; and it may be said with reference to all except four of the geological formations that there is seen some tendency to inverse correlation between the incidence of goiter and the radiation index. In

TABLE 4.—*Notations from Examination of Charts 20 to 41* *

		Correlation Between		
Chart	Geological Formation	Radiation Index and Iodine Content of the Soil	Chart	Incidence of Goiter and Radiation Index (Inverse)
..	II			
.	VI / II	None	..	None (only two districts, with same radiation index)
20	III			
	VI / III	None	30	Some (only four districts)
21	IV			
	VI / IV	Some	31	Some (districts 13, 23 and 27 high in goiter)
			32	Some (district 7 low and district 27 high in goiter)
22	Vb			
	VI / Vb	Some	33	Some (district 7 low in goiter)
			34	Some (district 7 low in goiter)
23	Vm			
	VI / Vm	None	35	Some
24	Va	None	36	None
25	VIg	Some	37	Some
26	VIs	Some (a group of five districts in North Island low in iodine)	38	Some (districts 13, 23 and 28 high in goiter)
27	VIsw	None	39	None
28	VIds	None	40	None (only four districts; district 7 low, and district 23 high in goiter)
29	All geological formations	Some (districts 2 and 7 high in iodine)	41	Some (districts 2 and 7 low, and districts 23, 27, 28 and 29 high in goiter)

* Districts low in goiter (relatively high in iodine):

2. "The only inhabited area of basic plutonic rock in New Zealand" (Hercus, Benson and Carter).

7. The only district from which the samples of soil were predominantly from geological formation VIsw (swamp deposits from post-Tertiary sediments of fluvatile, marine or glacial origin); 19 samples.

Districts high in goiter:

13. "Not fully represented by the few soil samples and schools studied" (Hercus, Benson and Carter).

23. No comment.

27, 28 and 29. See comments of Hercus, Benson and Carter questioning the accuracy of the data for these districts.

each of the four geological formations excepted only a relatively small number of districts was represented. There is also seen some tendency to inverse correlation between the incidence of goiter and the radiation index of all the different geological formations taken as a group.

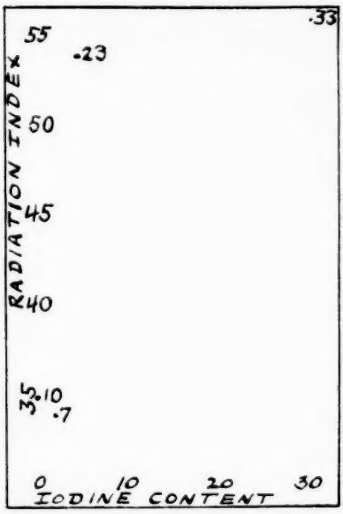

Chart 28.—The relation of the radiation index to the amount of iodine in the soils of geological formation VIds (dune sands from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

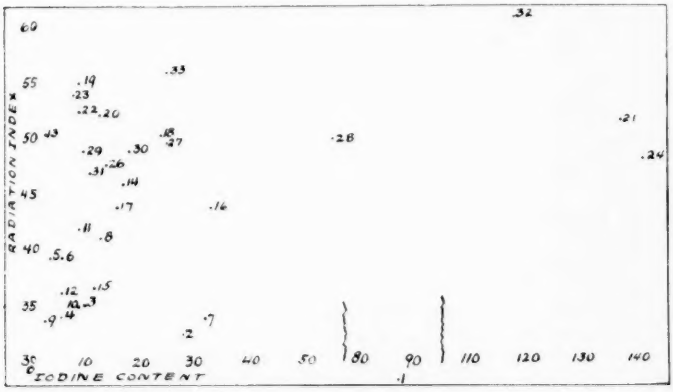

Chart 29.—The relation of the radiation index to the amount of iodine in the soils of all geological formations as reported by Hercus, Benson and Carter. The figures by dots denote districts.

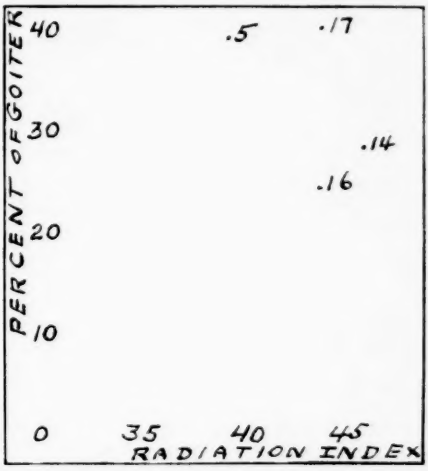

Chart 30.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soils from geological formations III (greywackes, argillites, etc., mostly rocks of Mesozoic but also in part of Paleozoic age) and $\frac{VI}{III}$ (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts.

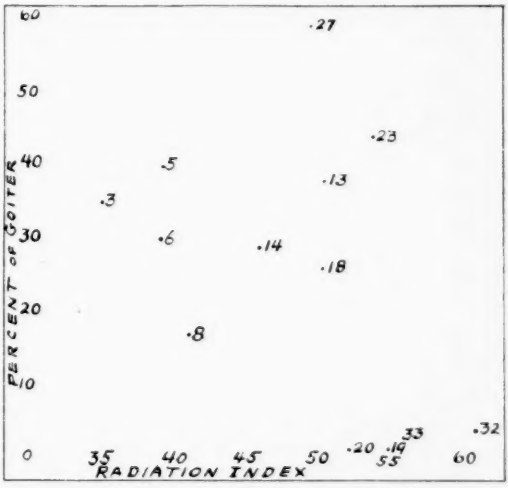

Chart 31.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation IV (younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke) according to Hercus, Benson and Carter. The figures by dots denote districts.

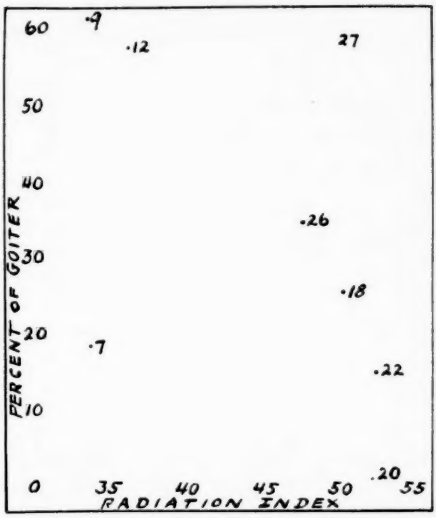

Chart 32.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation $\frac{VI}{IV}$ (younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke and underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts.

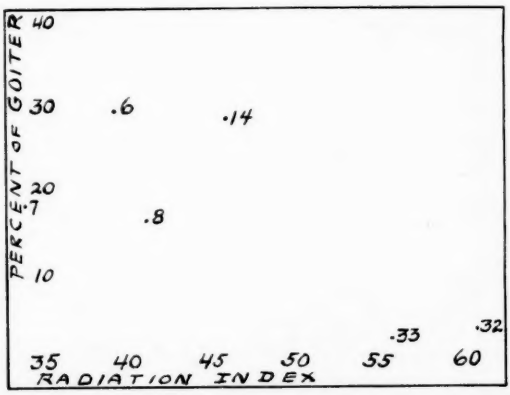

Chart 33.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation Vb (volcanic rocks which are basic-basaltic), according to Hercus, Benson and Carter. The figures by dots denote districts.

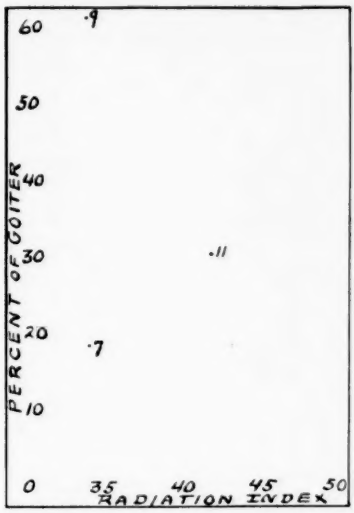

Chart 34.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation $\frac{VI}{Vb}$ (volcanic rocks which are basic-basaltic and underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts.

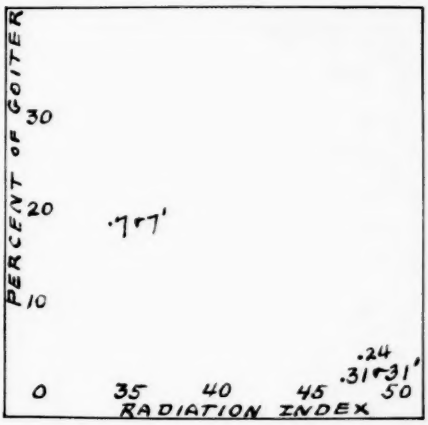

Chart 35.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formations Vm (volcanic rocks that are intermediate-andesite) and $\frac{VI}{Vm}$ (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ′ by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

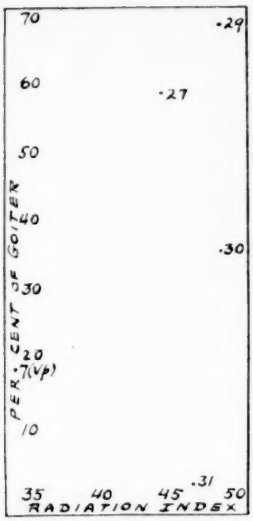

Chart 36.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation Va (volcanic rocks that are acid-rhyolite, rhyolite tuff and pumice or siliceous dacites), according to Hercus, Benson and Carter. The figures by dots denote districts.

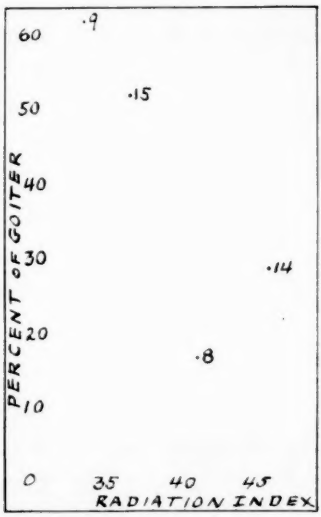

Chart 37.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation VIg (gravel from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

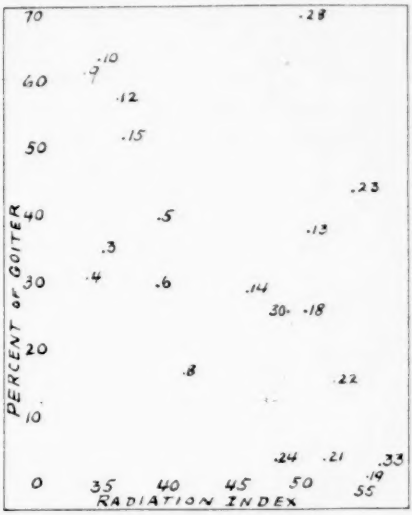

Chart 38.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation VIs (silts—mixed mud and sand—from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

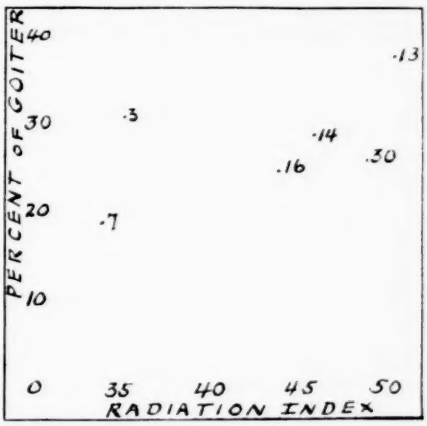

Chart 39.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation VIsw (swamp deposits from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

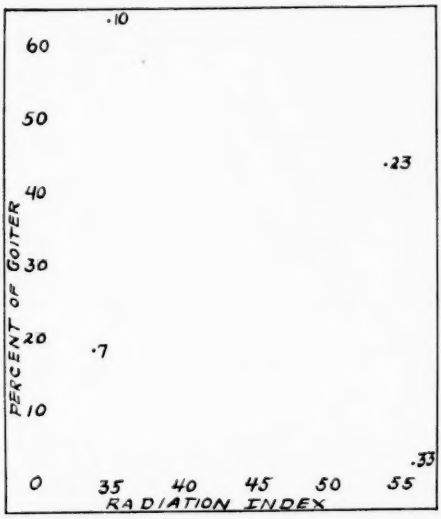

Chart 40.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation VIds (dune sands from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

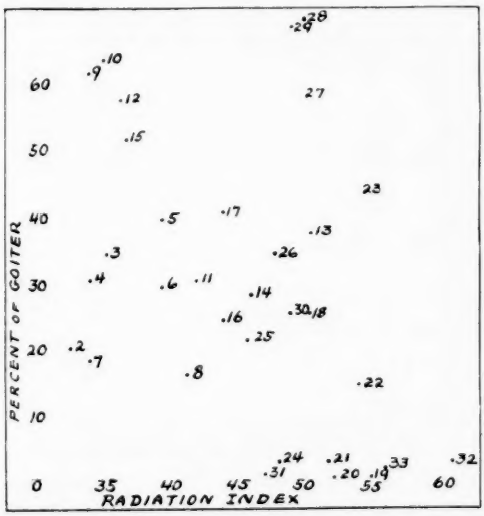

Chart 41.—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from all geological formations as reported by Hercus, Benson and Carter. The figures by dots denote districts.

The correlation referred to between the radiation index and the iodine content of the soil is direct, and that between the incidence of goiter and the radiation index is inverse, as is the correlation between the incidence of goiter and the iodine content of the soil. It appears, therefore, that in New Zealand solar radiation tends to decrease the incidence of endemic goiter.

CONCLUSIONS

The data in this section appear to support the conclusions in the two former sections dealing with endemic goiter in the United States and in India, respectively; namely, that a deficiency in solar radiation tends to a deficiency of the iodine content of the thyroid gland due to a lack of irradiation of the air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of endemic goiter.

In addition, with regard to several different geological formations in New Zealand, the iodine content of the soil appears to be roughly in proportion to solar radiation.

With regard to at least one type of geological formation (silts—mixed mud and sand—from post-Tertiary sediments of fluvatile, marine or glacial origin), the districts with a low iodine content of the soil derived from this geological formation (less than 13 parts in 10^7) show an incidence of endemic goiter in fairly close inverse proportion to the radiation index, suggesting that solar radiation tends to decrease the prevalence of endemic goiter in areas where the iodine content of the soil is low.

IV. THE RELATION OF SOLAR RADIATION TO THE IODINE OF POTATOES AND THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN SOUTH CAROLINA

In sections I and II data were presented that appeared to suggest that a deficiency of solar radiation tends to an increased prevalence of endemic goiter, and in section III data were presented that not only support this conclusion, but in addition seem to suggest that, in New Zealand, the iodine content of the soil appears to be roughly in proportion to solar radiation. In this section, certain data relating to South Carolina as reported by Remington [39] and others will be examined with reference to the relation between solar radiation, the iodine of vegetables and goiter.

39. Remington, R. E.: A Nutritional Research in the South, South. M. J. **24**:49 (Jan.) 1931.

Chart 42 shows topographical and soil areas in South Carolina;[39] table 5, goiter in South Carolina school children,[40] and table 6, the iodine content of potatoes in relation to the distance from the sea.[41]

Data on solar radiation in South Carolina are available in the reports of the United States Weather Bureau as percentage of possible sunshine, summarized for the period of observation to and including 1920 in Bulletin W, and as "cloudiness" in the *Monthly Weather Review* of the bureau. The definition of these two terms and the methods of recording, as described by the bureau, are given elsewhere,[1] as also a notation to the effect that, though the percentage of sunshine and that of cloudiness are inversely related, they are not exactly so according to the methods of recording. On this account, in the present article, a mean of the two values, percentage of possible sunshine and cloudiness (reversed)[42] has

TABLE 5.—*Goiter in the School Children of South Carolina*

	Number Examined	Percentage Enlarged
Coastal counties	5,684	2.7
Upper pine and sand hill counties	6,493	3.3
Piedmont counties	5,423	1.7

TABLE 6.—*Iodine Content of Potatoes in Relation to the Distance from the Sea*

Distance from Sea in Miles	Number of Samples	Iodine Content (Average)
0– 50	19	180
50–100	18	213
100–150	15	223
150–200	16	249
200	4	266

been used to represent solar radiation at the three South Carolina Weather Bureau stations for which the complete data are available: Charleston, in the coastal region and representing the Lower Pine Belt; Columbia, in the Sand Hills and Upper Pine Belt, and Greenville, in the Piedmont Region.

40. Hayne, J. A.: Endemic Goiter and Its Relation to Iodine Content of Food, Am. J. Pub. Health **19**:1111 (Oct.) 1929. Remington (footnote 39).

41. "The potato . . . was chosen for this comparison because it is easily obtained everywhere, easily stored and shipped, and easily handled in the laboratory" (Remington, R. E.; Culp, F. B., and von Kolnitz, H.: The Potato as an Index of Iodine Distribution, J. Am. Chem. Soc. **51**:2942, 1929). Remington (footnote 39).

42. The figures used for cloudiness represent the average for the decade 1920-1929, inclusive, and the scale is, arbitrarily, twice that for possible sunshine. Cloudiness for the month of May at Columbia is represented by the figures for nine years only. The figures for possible sunshine, taken from Bulletin W, cover observations at Charleston for twenty-four years; at Columbia, for sixteen years, but at Greenville for only three, and sometimes four, years.

Chart 43 shows the solar radiation for the months of December, January and February to be greatest at Greenville, intermediate at Charleston and least at Columbia. This order is inverse to that of the incidence of goiter as reported by Hayne.

Chart 43 also shows the solar radiation for the months of July, August and September to be greatest at Greenville, intermediate at Columbia and least at Charleston. This order is the same as that of the iodine content of potatoes, as reported by Remington and his co-workers.

If this observation of a relationship between the iodine content of vegetables and solar radiation should prove on further investigation to

Chart 42.—Topographical and soil areas in South Carolina. (After Remington and his co-workers.)

hold more generally, it would seem to be essentially linked with the tendency observed (section III) of the iodine content of the soil of New Zealand, as reported by Hercus, Benson and Carter, to be roughly in proportion to solar radiation at the time of the year for which the comparison was made (June—winter in New Zealand), regarding the soil as the soil of plant food.

That solar radiation during the months of July, August and September (in the north temperate zone) may have special significance in relation to the iodine content of vegetables is suggested by the following reported observations.

Von Fellenberg [43] in 1923 determined the iodine content of the salt from Schweizerhalle. In August, the salt contained no detectable iodine. On September 4 it contained 0.8 part per billion, and in October it rose to 7.7 parts per billion.

Veil and Sturm [43] studied the variations in the iodine content of blood. In the late summer and fall it was 128 parts per billion, and in the winter, 83 parts per billion.

Summer cabbage fed to rabbits had a much less marked goiter-producing tendency than cabbage grown in the late autumn.[17] Rabbits brought into the laboratory in the late fall or winter developed goiter

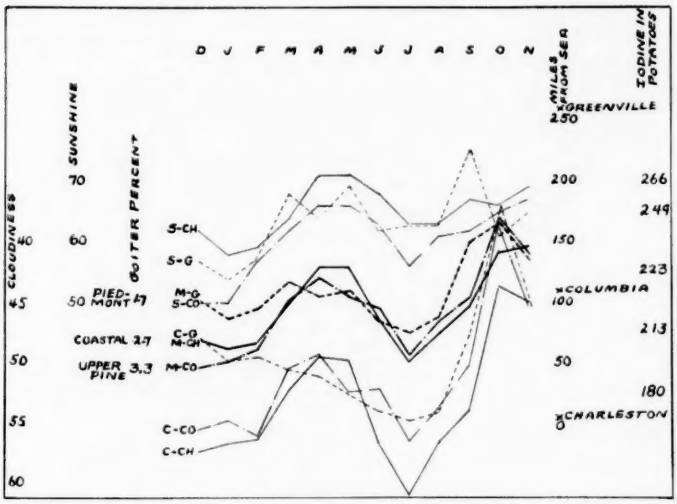

Chart 43.—The solar radiation in South Carolina, by months. Curve *S-CH* indicates sunshine at Charleston; *S-CO*, sunshine at Columbia; *S-G*, sunshine at Greenville; *C-CH*, cloudiness at Charleston; *C-CO*, cloudiness at Columbia; *C-G*, cloudiness at Greenville; *M-CH*, mean of sunshine and cloudiness at Charleston; *M-CO*, mean of sunshine and cloudiness at Columbia; *M-G*, mean of sunshine and cloudiness at Greenville. The chart also shows the percentage of goiter in school children in the three topographic and soil areas (not scaled), the iodine content of potatoes in relation to distance from the sea and the distance from the sea of Charleston, Columbia and Greenville, respectively.

on a cabbage diet much more promptly than those brought in during the spring and summer.[16] Similarly, some of the large goiters tended to decrease in size slightly during the spring and summer.

43. Quoted by McClendon, J. F.: The Distribution of Iodine with Special Reference to Goiter, Physiol. Rev. **7**:189, 1927.

The iodine content of the thyroid gland is low in the early spring,[28] and goiter shows its highest incidence in India at the end of the rainy season.[44]

CONCLUSIONS

The data in this section appear to support the conclusions in the three former sections dealing with endemic goiter in the United States, India and New Zealand, respectively; namely, that a deficiency of solar radiation tends to a deficiency of the iodine content of the thyroid gland due to a lack of irradiation of the air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of goiter.

In addition, the iodine content of potatoes in districts of South Carolina, according to the distance from the sea, appears to vary with solar radiation during the late summer months, suggesting that solar radiation at this period of the year may have some influence on the iodine content of vegetables.

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44. McCarrison (footnote 31). Stott, Bhatia, Lal and Rai (footnote 33).

EFFECTS OF PROLONGED LIVER DIETARY IN PERNICIOUS ANEMIA

CASE REPORTS OF THREE PATIENTS RECEIVING LIVER THERAPY FOR NINE AND A HALF, EIGHT AND SEVEN YEARS, RESPECTIVELY

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More than ten years ago, Gibson and Howard [1] undertook a study of the chemical pathology and metabolism of pernicious anemia. Eleven cases along with four cases of other types of anemia were reported. An experimental diet consisting of fruits, green vegetables, lima beans, egg yolk and liver (100 Gm. or more daily) was employed. This diet induced favorable retention of iron and nitrogen and enhanced the remissions in pernicious anemia; beginning in the fall of 1921 it was prescribed as a routine measure in our service, along with other recognized measures employed to promote hematogenesis. The patients were given specific dietary instruction when discharged. The use of such a diet in the therapy for pernicious anemia was urged in that report.

During the present year, three of our patients who received the liver diet before liver therapy was accepted generally as a specific therapeutic procedure have returned to this hospital. One of them was included in the original experimental group (1921), the second first received liver therapy in the summer of 1923 and the third, in the spring of 1924. It seems of interest to give a description of these patients when they were seen initially, their history in the interim, and the present status of the disease.

Of the original eleven patients studied by the senior author, seven have died and three have not been traced. At that time it was difficult to convince both the patients and their own home physicians of the importance of the dietary therapy. One patient (case 9) who followed the instructions faithfully died in December, 1929, of a cerebral hemorrhage; there had been no recurrence of the anemia.

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1. Gibson, R. B., and Howard, C. P.: Metabolic Studies in Pernicious Anemia, Arch. Int. Med. **32**:1 (July) 1923. A preliminary report was read before the Central Interurban Clinical Club at Iowa City, April 23, 1921.

REPORT OF CASES

CASE 1.—*History.*—W. D., a white man, aged 55, entered the University Hospital on Oct. 13, 1921, because of gastric distress, weakness, and numbness of the hands and feet. The gastric distress had been present for several years, but had increased in severity during the two years prior to admission. The weakness had become noticeable at about the time that the gastric distress had increased, and had progressed so rapidly that he had not been able to work for the preceding

TABLE 1.—*Regeneration of the Blood of W. D. on Liver Dietary*

Admission	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Comment
First	10/ 5/21	54	2,030,000	4,120	Polymorphonuclears 59, lymphocytes 40, basophils 1
	10/13/21	65	2,180,000	5,200	
	10/24/21	70	2,620,000	4,800	Transferred to metabolism ward
	10/31/21	70	3,260,000	5,200	
	11/ 8/21	70	3,180,000	4,100	In metabolism ward
	11/17/21	..	3,880,000	6,050	
	11/25/21	80	4,050,000	4,050	
	12/ 5/21	75	3,920,000	5,800	Polymorphonuclears 74, lymphocytes 22, transitionals 4
Second	11/ 3/22	87	2,600,000	3,650	Polymorphonuclears 66, lymphocytes 31, large monocytes 2, transitionals 1
	11/ 6/22	89	2,970,000	3,000	
	11/10/22	90	2,860,000	.....	
	11/15/22	80	2,800,000	5,100	
	11/16/22	..	.....	.....	Transfusion
	11/18/22	82	3,000,000	9,000	
	11/19/22	85	3,400,000	.....	
	11/27/22	104	4,100,000	.....	
	12/ 6/22	..	3,940,000	.....	
	12/12/22	104	3,700,000	.....	
	12/17/22	..	3,450,000	.....	
	12/19/22	..	.....	.....	Transfusion
	12/22/22	..	3,930,000	6,600	
	12/26/22	100	4,500,000	.....	
	1/ 1/23	97	4,670,000	.....	
Third	6/12/27	12	610,000	3,200	
	6/15/27	..	.....	.....	Transfusion
	6/17/27	16	820,000	.....	
	6/22/27	30	1,970,000	.....	
	6/24/27	32	1,880,000	.....	
	6/29/27	35	2,150,000	5,150	
	7/ 4/27	40	2,770,000	.....	
	7/ 9/27	45	2,610,000	.....	
	7/16/27	60	3,240,000	.....	
	7/19/27	63	3,580,000	.....	
	7/22/27	71	4,140,000	5,800	
	7/27/27	73	4,090,000	.....	

eight months. One month prior to admission to the hospital, the patient had several attacks of diarrhea and began to notice numbness and clumsiness of the extremities.

Examination.—There was moderate pallor and slight icterus of the skin. The mucous membranes were pale, and the tongue was smooth and atrophic. The lungs were normal. The heart was of normal size, with a systolic murmur at the apex. The blood pressure was 90 systolic and 50 diastolic. The spleen could just be felt below the left costal margin. Neurologic examination revealed subacute combined sclerosis of the cord. Urinalysis gave normal results. Analysis of the gastric contents showed an absence of free hydrochloric acid and a total acidity of 9. The stomach and duodenum appeared normal on roentgen examination. The blood smears showed a marked variation in the size and shape of the red cells with macrocytes predominating.

Course.—The patient was given the diet for pernicious anemia with liver at the time of admission. The blood counts and hemoglobin readings for this and each subsequent admission are given in table 1. He improved markedly, and he was discharged with dietary instructions on Dec. 15, 1921.

Second Admission.—On Nov. 3, 1922, the patient returned to the hospital, stating that he had followed the instructions carefully for four months; his weight had increased from 129 to 156 pounds (58.5 to 70.8 Kg.), and his general condition had been good. He then became negligent; the gastric distress reappeared, and he had an attack of diarrhea. The physical findings were similar to those on the previous admission. He was given the same diet, but during this admission he received two transfusions of blood. On Jan. 2, 1923, he was again discharged with the same dietary instructions as before, and pills of ferrous carbonate, U. S. P., solution of potassium arsenite and dilute hydrochloric acid were prescribed.

Third Admission.—Subsequent to his discharge in 1923, there was a remission that lasted for three years. During this time he followed his dietary instructions faithfully, and was able to do hard work on the farm. Later he became careless about taking liver, and in the spring of 1926, a recurrence of the anemia, jaundice and gastric distress occurred. He then improved somewhat, but was able to do only light work. For the eight weeks prior to the third admission he became progressively worse; the pallor, jaundice, weakness and gastric distress recurred. He returned to the hospital on June 12, with an erythrocyte count of 610,000. The gastric contents contained no free acid, and the total acidity was 0. There was pallanesthesia and lingual atrophy. He was again given the diet for pernicious anemia, pills of ferrous carbonate, U. S. P., solution of potassium arsenite and hydrochloric acid. Because of the extreme anemia he received a transfusion of blood three days after admission. He was discharged on July 26, 1927, greatly improved, and with the instructions and medication given him previously.

Fourth Admission.—On March 20, 1931, the patient returned to the University Hospital at our request. Since his discharge in 1927, he had followed the diet closely and had persistently eaten liver. During this time he had been able to do the heaviest farm work without difficulty. There was slight numbness of the extremities, but this was not as troublesome as it had been on his first admission. He was now 64 years of age, well developed and nourished and without pallor or icterus. The tongue was somewhat smooth. The heart was normal in size, and there were no murmurs. The blood pressure was 126 systolic and 74 diastolic. The liver and spleen could not be felt. The neurologic findings were unchanged. The urine was normal. The gastric contents contained no free acid even after the administration of histamine, and the patient complained of gastric distress when hydrochloric acid was not given with his meals. Examination of the blood showed: hemoglobin, 93 per cent; erythrocytes, 4,490,000; leukocytes, 5,400, and reticulocytes, 1.4 per cent. A test for renal function showed a variation in specific gravity of from 1.008 to 1.020; the day volume of urine was 870 cc., the night volume, 860 cc., and 72 per cent of phenolsulphonphthalein was excreted in two hours. Chemical examination of the blood gave normal results.

CASE 2.—*History.*—W. H., a white man, aged 34 years, was admitted to the University Hospital on June 9, 1923, complaining of loss of weight and strength, shortness of breath and occasional edema of the ankles. The initial attack had occurred in November of the preceding year.

Examination.—On admission there was marked pallor and slight icterus of the skin. The gums bled slightly, and there was distinct atrophy of the tongue. The liver and spleen were palpable. The pulse was 120, and the blood pressure, 116

systolic and 56 diastolic. Examination of the blood showed: 29 per cent of hemoglobin, 730,000 erythrocytes and 3,100 leukocytes, with 39 per cent of lymphocytes. Pallesthesia was 50 per cent of normal over the shins. Two-point discrimination and knee jerks were diminished. Gastric analysis showed an absence of free acid and a total acidity of only 4. The excretion of urobilin was increased. The patient was placed on the diet for pernicious anemia and given dilute hydrochloric acid and solution of potassium arsenate and pills of ferrous carbonate, U. S. P. He received two transfusions. Improvement was rapid, and the patient gained 6 pounds (3.6 Kg.) in weight while he was in the hospital. He was discharged on July 24, 1923, with instructions to follow the prescribed diet and medication. At that time hemoglobin was 72 per cent; erythrocytes, 4,220,000, and leukocytes 6,200 (table 2).

TABLE 2.—*Regeneration of the Blood of W. H. on Liver Dietary*

Admission	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Comment
First	6/ 9/23	29	730,000	3,100	
	6/11/23	..	.....	.....	Transfusion
	6/13/23	35	1,340,000	.....	
	6/18/23	..	.....	.....	Transfusion
	6/21/23	30	2,230,000	.....	
	6/30/23	65	2,940,000	.....	
	7/ 6/23	67	3,320,000	7,800	
	7/12/23	68	3,380,000	.....	
	7/18/23	68	3,720,000	.....	
	7/24/23	72	4,220,000	6,200	
Second	11/10/24	55	2,150,000	5,150	
	11/15/24	..	.....	.....	Transfusion
	11/19/24	55	2,220,000	4,300	
	11/25/24	71	2,880,000	.....	
	11/30/24	75	2,880,000	5,900	
	12/ 6/24	80	3,470,000	5,000	
Third	7/23/31	52	2,600,000	7,500	General diet
	7/25/31	..	.....	.....	Reticulocytes, 0.6; ventriculin started
	7/30/31	60	2,645,000	6,000	Reticulocytes, 13.4
	7/31/31	..	.....	.....	Reticulocytes, 17
	8/ 3/31	75	3,180,000	.....	Reticulocytes, 3
	8/ 6/31	78	3,150,000	.....	
	8/13/31	79	3,280,000	8,300	Discharged

Second Admission.—The patient was admitted to the hospital again on Nov. 10, 1924. He had followed his instructions carefully since his discharge, particularly in regard to eating liver and meat, which had been impressed on him. He had felt well, resumed his occupation doing heavy labor, and had missed only two days of work until five weeks before this admission, when influenza developed. He apparently recovered from this infection in a few days, but anemia developed, and he returned to our service. The patient's skin was icteroid and pale. The tongue was atrophic. The physical and neurologic findings were similar to those noted on the preceding admission. The hemoglobin was 55 per cent; erythrocytes, 2,150,000, and leukocytes, 5,150, with 50 per cent lymphocytes. The blood smear showed the typical picture of pernicious anemia. The patient was again given the diet for pernicious anemia and dilute hydrochloric acid, with solution of potassium arsenite and pills of ferrous carbonate, U. S. P. He received one transfusion. He was discharged on December 9, much improved; the last examination of the blood (December 6) showed: hemoglobin, 80 per cent; erythrocytes, 3,470,000, and leukocytes, 5,000.

Third Admission.—The patient was admitted again on July 23, 1931, with anemia which had developed after a remission of almost six and a half years. Since his second admission he had eaten meat and liver practically every day. He had been able to work hard and had but little illness until the present condition. About four months before this admission, he "turned against liver" and had to discontinue it. Two months later he became weak, short of breath and noticed a tingling sensation in the extremities. He became so weak that he had to remain in bed for two months prior to admission to the hospital. The glossitis had persisted, and there was a slight icteric tint to the skin. The spleen was palpable, but the liver was not enlarged. Although the patient complained of more numbness and tingling in the extremities on this last admission, the vibratory sense, the two-point discrimination and the sense of position were about normal. The patellar and tendo achillis reflexes were absent. Analysis of the gastric contents showed an achlorhydria even after the administration of histamine. A test for renal function showed that the specific gravity varied from 1.013 to 1.016, with a day output of 625 cc. and a night output of 550 cc. The excretion of dye was normal. The uric acid was 6.6 mg., the urea nitrogen, 23.1 mg. and the creatinine, 1 mg. per hundred cubic centimeters. The patient was given ventriculin and responded satisfactorily to this therapy. The blood counts are given in table 2.

Case 3.—*History.*—E. K., a white man, aged 53, was admitted to the University Hospital in April, 1924. Five years previous to this (1919) he had a period of weakness associated with anemia, which was followed by a complete remission lasting until 1921, when he had a similar spell of weakness with numbness of the hands and feet, some edema of the ankles, a sore tongue and gastric distress. Since 1921, he had these attacks every fall, each one being more severe than the preceding one. The relapse that brought the patient to the hospital began six months prior to admission.

Examination showed a marked pallor with an icteric tint to the skin and sclerae, but the general nutrition was surprisingly good. The tongue was pale and atrophic. There were a hemic murmur over the heart and a slight pitting edema of the feet and ankles. The edge of the spleen was just palpable. Neurologic examination showed a subacute combined sclerosis of the cord.

There was 20 per cent hemoglobin. The erythrocytes numbered 930,000 and showed marked anisocytosis, poikilocytosis, polychromatophilia and stippling. Several megalocytes were seen on the smear. (The complete series of blood counts is given in table 3.) There was no free hydrochloric acid in the gastric contents, and a series of roentgenograms of the gastro-intestinal tract showed a normal condition. Urobilin was increased in the urine and stools. The patient was placed on the regular diet for pernicious anemia, and given, in addition, dilute hydrochloric acid and solution of potassium arsenite. He was discharged on June 23, 1924, with instructions to live on the aforementioned diet, eating liver every day.

Second Admission.—The patient returned to the hospital in February, 1925, with essentially the same physical findings as on the previous admission. He had not followed his dietary instructions after the first two months following his discharge and began to notice increasing weakness two months prior to his return. He was given the same diet. The blood count on admission was: hemoglobin, 53 per cent; erythrocytes, 2,050,000, and leukocytes, 4,400. At the time of discharge on April 10, 1924, the hemoglobin was 79 per cent and the erythrocytes, 3,000,000.

Third Admission.—Following discharge, the patient felt well until September, 1925, when he had an attack of diarrhea associated with severe abdominal cramps and a temperature of 102 F. The abdominal distress persisted, and he gradually

became weaker. He had taken no medication since early the previous fall. When admitted to the hospital (March 9, 1926) the blood showed 39 per cent hemoglobin, 1,740,000 red blood cells and 2,000 white blood cells. Two transfusions of blood were administered during this admission. He was discharged on April 26, 1926, with 55 per cent hemoglobin, 3,220,000 red blood cells and 2,900 white blood cells.

Fourth Admission.—The patient became convinced of the efficacy of the diet and ate cooked liver regularly, eating about one-fourth pound (113.4 Gm.) daily and doing without it only occasionally for very short periods. He had had no symptoms relative to the anemia since his discharge from the hospital in 1926, and had been doing heavy work regularly. The neurologic symptoms remained practically stationary. Seven weeks prior to admission, he first noticed polydypsia and polyuria, and glycosuria was found. Five days prior to admission he became comatose and received treatment at home, but he was given no insulin after recovering from the diabetic coma. He was sent to the hospital for diabetic management. He was well nourished, without pallor or icteric color. There was some sclerosis of the

TABLE 3.—*Regeneration of the Blood of E. K., on Liver Dietary*

Admission	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Comment
First	4/16/24	20	930,000	2,600	
	4/23/24	28	1,130,000	3,700	
	4/28/24	54	2,370,000	5,900	
	5/ 4/24	55	2,650,000	6,000	
	5/10/24	85	4,200,000	6,000	
	5/12/24	..	.....	.....	Fever; severe stomatitis; unexplained
	5/14/24	90	4,230,000	5,300	
	5/24/24	60	2,600,000	4,000	
	5/29/24	80	3,600,000	4,000	
	6/ 2/24	..	.....	.....	Fever; temperature 104 F.
	6/ 5/24	76	3,570,000	4,300	
	6/14/24	80	3,850,000	6,700	
	6/21/24	85	3,850,000	7,000	

vessels of the fundi, and the brachial vessels were moderately sclerotic. The tongue was smooth and reddened, but it was not sore. The lungs were normal. The heart was normal in size with a faint systolic murmur at the apex; the blood pressure was 128 systolic and 64 diastolic. The liver was not enlarged, but the edge of the spleen could just be felt beneath the left costal margin. No pulsation could be felt in either dorsalis pedis artery, but a good pulsation was felt in the posterior tibial arteries. The neurologic findings were unchanged. There were areas of leukoderma over the inner aspect of both wrists.

On admission there was 4 plus glycosuria, with a few casts and a trace of acetone. The urobilin in the urine was not increased. The modified Mosenthal test for renal function showed that the specific gravity varied from 1.003 to 1.016, with a normal ratio between the day and night output. Chemical examination of the blood showed: uric acid, 4.2 mg.; urea nitrogen, 13.3 mg., and creatinine, 1 mg. per hundred cubic centimeters. The van den Bergh test gave normal results, and the Wassermann test was negative. The blood sugar was 349 mg. per hundred cubic centimeters. The diabetes was controlled by the use of gradually decreasing doses of insulin, and on discharge the patient was receiving 10 units in the morning and 4 at night. The blood count showed 96 per cent hemoglobin (Sahli), 4,120,000 red blood cells, and 7,800 white blood cells, with a normal differential count. The hematocrit reading was 38 per cent. There was no free hydrochloric acid in the gastric contents.

SUMMARY

Case reports of three patients with pernicious anemia for whom a liver dietary was prescribed from 1921 to 1924 along with other therapeutic measures to enhance and maintain the remissions are presented. These patients are undoubtedly the longest survivors among patients treated with liver for pernicious anemia whose records have been followed. While the liver dietary has been neglected at times by two patients (those in cases 1 and 3) with recurrence of the anemia, subsequent adherence to the dietary instructions has resulted in prolonged remissions, recovery of normal body strength and return to their occupations. A third patient (case 2) followed his dietary prescription consistently until four months previous to the last admission to the hospital (July, 1931) with the resulting attack of the anemia; a previous attack in 1924 followed an acute infection said to be influenza, so his remission had lasted six and one-half years. As has been observed in other cases by later workers with liver and active extracts (Minot,[2] Sturgis,[3] and others), the neurologic symptoms, the glossitis and achlorhydria in our three patients with pernicious anemia have remained essentially unimproved. For two of our patients, renal function is satisfactory; renal damage is evident in case 2, and possible injury attributable to the daily nucleoprotein intake cannot be excluded. But because of the progress all three patients have made and because of dietary factors in liver other than the substance effecting regeneration of the blood,[4] we feel that the dietary treatment of pernicious anemia should not be neglected, even though liver extracts are employed to induce and maintain the remissions.

2. Minot, G. R., and Murphy, W. B.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. A. M. A. **89**:759 (Sept. 3) 1927.

3. Sturgis, C. C.; Isaacs, R., and Riddle, M. C.: The Treatment of Pernicious Anemia by Liver Feeding, Surg., Gynec. & Obst. **50**:234, 1930.

4. Dakin, H. D.; West, R., and Howe, M.: Further Note on a Substance in Liver Active in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **28**:2, 1930.

MYOCARDIAL INFARCTION OR GROSS FIBROSIS

ANALYSIS OF ONE HUNDRED NECROPSIES

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The cases in this series were selected on the basis of gross postmortem evidence of either recent infarction or fairly well circumscribed patches of fibrosis in the heart muscle. The fibrotic patches were all gross and were readily seen macroscopically; they were usually well marginated. The large majority averaged at least 3 cm. in the largest diameter. It is believed that these fibrotic patches or scars in most cases probably represented areas of old infarction, particularly in view of the high incidence of associated coronary sclerosis. At any rate, as, regardless of their etiology, they presented a definite pathologic entity, they were grouped together in this series.

The one hundred cases selected comprised all cases in which the heart showed the aforementioned lesions in a series of nine hundred and forty-two necropsies performed at City Hospital from Jan. 3, 1928, to May 1, 1931. Thirty-two of the one hundred cases showed definite recent infarction, twenty-three of which also gave evidence of old myocardial scarring. The remaining sixty-eight cases were those that showed gross fibrosis alone. Thus 3.4 per cent of all autopsies performed during the period mentioned showed recent infarction, and 10.6 per cent showed either recent infarction or gross fibrosis, or both. This may seem an unusually high incidence, but the material at this hospital is in large part of a chronic nature, and includes a large number of patients past middle life suffering from arteriosclerotic heart disease.

INCIDENCE

Sex and Race.—Eighty-three patients were males, seventeen females, a ratio of almost 5:1. Parkinson and Bedford [1] in their autopsies performed in cases of cardiac infarction or mortal coronary thrombosis, found seventy-two males to eleven females.

From the Department of Pathology, City Hospital, W.I., Department of Hospitals.

1. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:4, 1928.

The racial distribution was as follows: Of the eighty-one white persons, sixty-six were males and fifteen females. Of the eighteen colored persons sixteen were males and two females. There was a Chinese male.

Age.—The average age in all cases was 60.8 years. The distribution according to decades is indicated in table 1. In his outstanding monograph on coronary thrombosis, Levine [2] recorded forty-six autopsies, thirty-one performed on males and fifteen on females. The average age of the males was 61.3 years; that of the females, 61.8 years.

The youngest patient in our series was 28, the oldest 83 years old. The former case is worthy of note as being indicative of the early age at which coronary sclerosis and fibrotic patches of the type described may be found. The patient in this case died of uremia in the course of a chronic glomerulonephritis, with a superimposed terminal streptococcal bacteremia. At autopsy the heart weighed 450 Gm., and in the

TABLE 1.—*Age Distribution According to Decades*

Age	Number of Cases
20 to 29	1
30 to 39	2
40 to 49	10
50 to 59	23
60 to 69	41
70 to 79	20
80 to 89	2
Not recorded	1

septum midway between its midportion and apex there was a fairly large, irregular white scar, which did not present, however, on either the epicardial or the endocardial surface. The coronary vessels were patent throughout, but the left anterior descending branch showed marked arteriosclerosis with narrowing of its lumen in the upper third. The remainder of this vessel, as well as the other coronary branches, showed only slight changes.

WEIGHT OF HEARTS

The average weight of the hearts in the entire series was 519 Gm. The smallest heart weighed 200 Gm., the largest, 925 Gm. The smallest heart was that of a man of 83 who showed old fibrotic lesions, aneurysmal dilatation of the left ventricle and liquefaction necrosis of a recent infarct.

The number of cases in each weight group is indicated in table 2.

It is seen at a glance that the large majority of hearts showed definite hypertrophy. The part played by old infarctions or fibrosis in inducing

2. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8**:245, 1929.

hypertrophy of the rest of the heart muscle is a factor difficult to estimate because of the concomitant presence in most of the cases of other factors that may likewise have induced hypertrophy.

The average weight of the hearts in each decade is interesting to note and is indicated in table 3.

Though the differences here are not outstanding, there is nevertheless an appreciable decrease in weight after the fifth decade.

TABLE 2.—*Weight of Hearts in Series Reported*

Weight, Gm.	Number of Cases
200 to 299	4
300 to 399	16
400 to 499	18
500 to 599	15
600 to 699	22
700 to 799	10
800 to 899	3
Over 900	1
Not recorded	11

TABLE 3.—*Average Weight of Hearts in Each Decade*

Decade	Number of Cases	Average Weight of Heart, Gm.
20 to 29	1	450
30 to 39	2	550
40 to 49	9	600
50 to 59	21	540
60 to 69	36	523
70 to 79	17	453
80 to 89	2	325

LOCATION OF LESION

The thirty-two cases of recent infarction were distributed as follows:

Left ventricle	16 cases
Left ventricle and interventricular septum	10 cases
Interventricular septum	3 cases
Apex of both right and left ventricles	1 case
Right ventricle and septum	1 case
Right and left ventricles and septum	1 case

The two last mentioned cases were both instances of right coronary occlusion.

The associated old lesions in twenty-three of the thirty-two cases of recent infarction were distributed as follows:

Left ventricle	8 cases
Left ventricle and interventricular septum	9 cases
Interventricular septum	5 cases
Right ventricle	1 case

The lesions of old infarction or fibrosis were situated as follows:

Left ventricle	27 cases
Left ventricle and interventricular septum	24 cases
Interventricular septum	11 cases
Right and left ventricles	3 cases

In three cases the description was insufficient for localization.

Thus it is seen that the large majority of lesions were found in the left ventricle or in the left ventricle and adjoining septum. However, it is noteworthy that in fourteen cases the lesions were confined to the septum exclusively and, as in many cases there was no endocardial or pericardial involvement, the importance of examination of this portion of the heart muscle is emphasized.

CORONARY VESSELS

Sclerosis.—Twenty-one of the cases with recent infarction showed moderate to marked sclerosis of the coronary vessels; three, only slight sclerosis; three were reported as normal or with only minimal changes, while in five the description of the coronary vessels was lacking or inadequate.

Of the cases with old lesions, fifty-four showed moderate to marked sclerosis. In this group narrowing of the lumina of the vessels was marked in seventeen cases. Five cases showed only slight sclerosis. In four cases the vessels were normal or showed only minimal changes. In the remaining five cases, description was lacking or inadequate.

Thus of the ninety cases available for analysis, seventy-five, or approximately 83 per cent, showed moderate to marked sclerosis and eight, slight sclerosis, and in seven cases the vessels were practically normal grossly.

The sclerosis of the coronary vessels was by no means uniform in its distribution in all cases. It was often patchy throughout the same vessel, and in a few cases marked sclerosis was found in the left coronary artery and its branches with only minimal changes in the right coronary wall.

An interesting feature in one case was an aneurysmal dilatation of the right coronary artery.

Thrombosis.—Thrombosis of the coronary arteries was noted in thirteen, or 40.7 per cent, of the cases with recent infarction and in eleven, or 16.2 per cent, of the cases with old lesions. Levine reported thrombosis in twenty-three of his forty-six autopsies, while in twelve others occlusion was due to the narrowing of the lumen of an arteriosclerotic vessel.

In our series the situation of the thrombus was as follows:

Cases with recent infarction—	
Anterior descending artery	9 cases
Posterior descending artery	1 case
Right coronary artery	1 case
Both right and left coronary arteries	2 cases
Cases with old lesions—	
Anterior descending branch of left coronary artery	10 cases
Both right and left coronary arteries	1 case

Thus of the twenty-four cases in which coronary thrombosis could be demonstrated, the thrombosis occurred in the anterior descending coronary artery alone in nineteen cases and in conjunction with thrombosis elsewhere in the coronary circulation in three other cases.

In the case in which the right posterior descending coronary artery was thrombosed, the infarcted area involved the right ventricle and interventricular septum especially at the apex. In the wall of the right ventricle was a recent mural thrombus involving most of the apex. A small old lesion possibly of an old infarction was found in the wall of the left ventricle. This case also showed recent infarcted areas in both lungs.

In the other case of thrombosis of the right coronary artery the thrombus extended from just beyond the mouth of the artery to well toward the base of the left ventricle. The infarcted area coincided fairly well with the usual distribution of the right coronary artery. The posterior half of the interventricular septum was found to contain a large cavity filled with a fresh blood clot. This cavity extended into the adjacent ventricles, especially the right. Transection of the right ventricular wall revealed a yellow infarcted area with a hemorrhagic zone at its periphery in its posterior aspect. The posterior half of the left ventricle revealed a similar infarcted area. Unfortunately, the patient in this case died less than three hours after admission to the hospital, and so the available clinical data were scanty.

COMPLICATIONS

Mural ventricular thrombosis was noted in thirty-four cases. It occurred in sixteen, or 50 per cent, of the cases with recent infarction. In thirteen of these cases it was confined to the left ventricle; in the three remaining cases it involved both ventricles.

In the cases of old fibrosis, mural thrombosis was noted in eighteen, or 26.4 per cent. In seventeen of these cases, the condition was confined to the left ventricle and in one, to the right ventricle. In their series, Parkinson and Bedford reported the occurrence of intracardiac thrombosis in fourteen of eighty-three instances; Levine, in thirty-eight of his forty-six cases of coronary thrombosis.

Aneurysm of the left ventricle or distinct aneurysmal bulging was noted in five cases. Parkinson and Bedford likewise recorded five cases in their series of eighty-three. However, they also reported five cases with rupture of the heart. Levine found nine ruptured hearts in his series of forty-six cases. No cases of rupture of the ventricle were noted in this series.

Chronic adhesive pericarditis was noted in ten cases, only two of which were in the group with recent infarctions. In a case not included in the ten mentioned, acute suppurative pericarditis was associated with an old tuberculous lesion. Parkinson and Bedford reported eleven cases of pericarditis, an incidence of 13 per cent. Levine noted pericarditis in twenty-four of his forty-six cases.

Of the ten cases of pericarditis in the present series, mural ventricular thrombosis occurred in five.

Endocardial complication was thus much more common than epicardial; there were thirty-four cases of the former to ten of the latter.

Other interesting features were thrombosis of both the right and the left auricular appendages in two cases and of the right auricular appendage alone in one case.

One case previously described [3] as showing thrombosis of both the right and the left coronary arteries also showed a rupture of the left auricular wall.

RELATIONSHIP TO SYPHILIS

The Wassermann test was made for sixty-one of the eighty-two white patients. Only six had positive reactions. However in one case in which the Wassermann test was negative, and in five cases in which no test had been made, there was evidence of vascular syphilis at autopsy. Of the group of eighteen colored patients, four had positive Wassermann reactions and eleven negative ones. There was no report on the Wassermann test for three others. In this group three of the eleven cases in which the Wassermann test was negative showed evidence of vascular syphilis at autopsy.

The incidence of syphilis was thus higher in the colored group. The rôle of syphilis as an etiologic agent in infarction or fibrosis as described in this series is a questionable one. As the patients at this institution are drawn from the lower walks of life, a goodly number have syphilitic infections. In any event, in practically all the cases herein noted in which the Wassermann test was positive or evidence of vascular syphilis was found at autopsy, there was associated coronary sclerosis not syphilitic in nature.

3. Lisa, J. R., and Ring, A.: A Case of Occlusion of Both Coronary Arteries with Rupture of the Auricle, J. Lab. & Clin. Med. **16**:1083 (Aug.) 1931.

BLOOD PRESSURE AND ELECTROCARDIOGRAPHIC FINDINGS

Hypertension, the criterion of which was a systolic pressure of 150 or over, or a diastolic pressure of 100 or over, occurred in forty-five of seventy-three cases in which blood pressure readings were recorded, an incidence of approximately 60 per cent. Barnes and Ball,[4] using this criterion, noted hypertension in twenty-four of forty-two cases of myocardial infarction.

One or more electrocardiographic tracings were taken in twenty-four cases, eight with recent infarctions, six of which also showed old lesions. The findings are tabulated in the accompanying table. Digitalis, as a possible factor in causing changes in the tracings, was eliminated in all but three cases.

Rhythm	
Normal sinus rhythm	11 cases
Normal sinus rhythm with extrasystoles	7 cases
Auricular fibrillation	5 cases
Idioventricular rhythm	1 case
Conduction Time	
Normal in seventeen of eighteen cases with normal sinus rhythm.	
Axis Deviation	
Left axis deviation	19 cases
No axis deviation	5 cases
Q-R-S Complex	
Abnormality (including notching, slurring, widening or low voltage in one or more leads)	17 cases
Normal	7 cases
T Wave	
Abnormality of the T wave (including inversion, isoelectricity or diphasic form) in one or more leads was noted in twenty-three of the twenty-four cases.	

It is seen from the accompanying table that the most constant abnormality observed was that of the T wave. Willius and Barnes [5] noted T wave change in twenty-six of thirty-one cases of myocardial infarction. Left axis deviation was the next most frequent finding, occurring in nineteen of the twenty-four cases. Abnormality of the Q-R-S complex was frequent, occurring in seventeen cases. Pardee [6] noted an abnormal ventricular wave in 81 per cent of cases in which the clinical diagnosis was cardiac infarction. In our present series auricular fibrillation was noted in only five cases and complete block in one.

4. Barnes, A. R., and Ball, R. G.: Proc. Staff Meet., Mayo Clin. **5**:367 (Dec. 17) 1930.

5. Willius, F. A., and Barnes, A. R.: Myocardial Infarction: An Electrocardiographic Study, J. Lab. & Clin. Med. **10**:427 (March) 1925.

6. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, Am. J. M. Sc. **169**:270 (Feb.) 1925.

CLINICAL PICTURE AND IMMEDIATE CAUSE OF DEATH

A classification of the cases according to their outstanding symptomatology and clinical course revealed that they might be grouped into two major classes, namely: (1) cardiac and (2) noncardiac in which the clinical syndrome involved primarily some other organ.

There were fifty-six cases in the cardiac group. They could be somewhat arbitrarily divided according to outstanding symptomatology into the following groups: (*a*) anginal, (*b*) dyspneic and (*c*) congestive failure and (*d*) a combined group in which the clinical course was marked by a transition from one of the preceding groups to another. To illustrate the basis of this classification the following four cases are reported in brief.

Anginal Type.—In a white man, the onset of the condition occurred with sudden severe epigastric pain when he was 65 years old. Subsequently recurrent attacks of precordial pain and dyspnea developed; they lasted several days, occurred at fairly frequent intervals, and became more frequent. The blood pressure was 190 systolic and 140 diastolic. Death occurred during an anginal attack one year later. Autopsy revealed acute cardiac infarction with old fibrosis associated with coronary sclerosis.

Dyspneic Type.—In a white woman, aged 70, acute paroxysmal attacks of dyspnea, orthopnea and transient edema of the ankles developed. The blood pressure was 170 systolic and 90 diastolic. The attacks lasted from one to two days, with free intervals between. She died at the end of a dyspneic attack which had lasted for about a week. The cardiac condition was of five months' duration. Autopsy revealed an old cardiac infarction, coronary sclerosis and canalized thrombosis of the anterior descending artery.

Congestive Failure Type.—In a white woman, aged 66, the onset of the condition was gradual, with weakness, edema of the ankles and dyspnea on exertion, which later became orthopnea, and cyanosis and ascites developed; similar periods recurred, and the condition became more severe during the following year. Autopsy revealed chronic passive congestion of all organs, anasarca, pleural effusion, dilatation of the heart, coronary sclerosis and an old infarct.

Combined Type.—In a Negro the onset of the condition occurred at the age of 54, with cardiac decompensation, namely, edema of the ankles, enlarged heart, dyspnea and cyanosis. The condition improved under treatment. A few months later typical angina developed, with recovery. The patient died suddenly about a year after the onset of illness. Autopsy revealed old and recent cardiac infarction.

The causes of death in each of these groups are indicated in table 4.

The three remaining patients in the cardiac group died within three hours or sooner after admission. No histories could be obtained. The deaths were cardiac in type. No diagnoses were made. All three cases presented recent cardiac infarction at autopsy.

Twenty-three of the deaths in the cardiac group were due to recent cardiac infarction. The incidence of the latter condition was relatively higher in the anginal and dyspneic subgroups than in the congestive or combined groups. In fourteen of the twenty-three cases a clinical diag-

nosis of recent cardiac infarction was made. In the nine cases in which no diagnosis was made, three patients were in the hospital too short a period. In four others congestive failure obscured the sudden onset of increased dyspnea and cardiac collapse. In the two remaining cases no suggestive data in the histories or physical examinations suggested the diagnosis. One occurred in a man, aged 67, with diabetes and a history showing an anginal tendency, who, however, entered the hospital because of empyema. He was in a dying condition for a period of four days. Autopsy showed empyema and recent cardiac infarction. The other case occurred in a man, aged 60, with hemiplegia and motor aphasia and no antecedent cardiac history. Symptoms and signs of pneumonia developed, and the patient died within two weeks. Autopsy showed rheumatic endocarditis, mesenteric thrombosis, recent cardiac infarction and bronchopneumonia.

TABLE 4.—*Causes of Death in Each Group of Cases*

	Number of Cases	Cause of Death	Number of Cases
(a) Anginal	11	Recent cardiac infarction	7
		Acute infections	3
		Cerebral thrombosis	1
(b) Dyspneic	12	Recent cardiac infarction	6
		Acute infections	2
		Pulmonary thrombosis	1
		Cerebral hemorrhage	1
		Undetermined by autopsy	2
(c) Congestive failure	14	Recent cardiac infarction	3
		Congestive failure	6
		Pulmonary thrombosis	2
		Acute infections	3
(d) Combined	16	Recent cardiac infarction	4
		Congestive failure	4
		Acute infections	5
		Pulmonary thrombosis	2
		Undetermined by autopsy	1

There were forty-four cases in the noncardiac group. In these cases the clinical syndrome involved primarily some other organ, and there was no indication of any cardiac lesion except as a terminal event in a few. It is interesting to note that nineteen of these forty-four cases presented the picture of a neurologic condition.

Nine of the deaths in the noncardiac group were due to recent cardiac infarction. In five of these cases the clinical picture was clear enough to warrant its diagnosis. The remaining four cases are mentioned briefly. In a patient with a neurologic condition, signs and symptoms of pneumonia developed, and autopsy revealed cardiac infarction. A second patient with a neurologic condition, bedridden, died suddenly without preceding symptoms of cardiac disease. A third patient, aged 83, with recurrent urinary retention, suddenly became irrational, and an irregular pulse rate and profuse perspiration developed. Death occurred

three days later, a diagnosis of uremia being made. In the fourth patient with a hernia of long standing abdominal pain and vomiting developed three days before death. The clinical diagnosis was strangulation of hernia. Autopsy showed recent cardiac infarction and no strangulation.

Of the patients with fibrosis interpreted as a result of old cardiac infarction, the large majority gave no clinical history suggesting previous acute infarction. The symptom of precordial pain was absent frequently.

In all, there were twelve sudden deaths, eight due to recent cardiac infarction, one to pulmonary thrombosis and one to pulmonary hemorrhage in tuberculosis and two in which autopsy failed to reveal the cause of the sudden death. Both of the latter cases were acute infections, one subacute bacterial endocarditis and the other acute ascending cholangeitis.

SUMMARY

A series of one hundred autopsies showing myocardial infarction or gross myocardial fibrosis, constituting 10.6 per cent of nine hundred and forty-two autopsies performed, are analyzed. Thirty-two of these cases showed definite recent cardiac infarction while sixty-eight showed fibrotic patches, interpreted as probable old infarctions. Eighty-three were in males, seventeen in females. The average age of all patients was 60.8 years. The youngest was 28; the oldest 83. The average weight of the heart was 519 Gm. Most of the lesions were located in the left ventricular wall or involved the left ventricle and interventricular septum, but in fourteen cases the lesions were confined to the septum alone. Approximately 83 per cent showed moderate to marked coronary sclerosis. Coronary thrombosis was noted in twenty-four cases; in three there was thrombosis of both the left and the right coronary artery. Mural thrombosis occurred in thirty-four cases, in sixteen of which there had been recent infarction. Aneurysm of the left ventricle was noted in five cases; chronic adhesive pericarditis occurred in ten. Ten patients had positive Wassermann reactions while nine others showed evidence of vascular syphilis at autopsy. Hypertension occurred in approximately 60 per cent of the cases. In twenty-four cases in which electrocardiograms were taken, the most frequent change was abnormality of the T wave, which occurred in twenty-three. Seventeen cases showed abnormalities of the Q-R-S complex, five auricular fibrillation and one complete heart block. Fifty-six cases presented cardiac symptomatology, while in the remaining forty-four the symptoms were referred to some other organ. Eight of the twelve sudden deaths in the series were due to recent cardiac infarction.

CONCLUSIONS

1. Recent cardiac infarction and coarse myocardial fibrosis interpreted as healed infarction are extremely common observations at autopsy. They are usually associated with coronary sclerosis and cardiac hypertrophy.

2. Males are more frequently affected than females; the proportion is 5 : 1.

3. The average age is approximately 60 years, but there is a very wide variation.

4. Hypertension is present in approximately 60 per cent of the cases.

5. Only slightly more than one half of the patients presented clinical features of cardiac disease.

6. Change in the T wave and Q-R-S complex are the most frequent electrocardiographic abnormalities.

7. Patients presenting anginal or dyspneic syndromes are more prone to death from acute cardiac infarction than those with the congestive or combined type.

8. Of the noncardiac cases, approximately 20 per cent terminate with recent cardiac infarction. In approximately one half of the latter cardiac symptoms develop as a terminal event.

9. In the large majority of cases with coarse fibrosis interpreted as healed infarction there is no history of a previous cardiac accident.

BISMUTH DIURESIS AND THE BLOOD AND URINARY CHANGES UNDER CLINICAL CONDITIONS

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The efficiency of sodium bismuth tartrate as a clinical diuretic and antiedemic has been sufficiently demonstrated in previous studies.[1] It appeared desirable to throw light, if possible, on the mechanism of these actions. It was especially desired to ascertain if the tissues in general might be the seat of the bismuth action. This was tried by attempts to correlate the changes in the metabolites, especially the chlorides of the blood and urine, with the diuretic action. Such an attempt on healthy rabbits indicated a tissue action of the bismuth.[2] The same was found to be true not only for bismuth, but also for theophylline, and possibly digitalis, in human subjects discussed in a preliminary report.[3] This paper presents various data and details of the results in patients with and without edema receiving bismuth.

METHODS

The results with bismuth were obtained in a total of fifteen different patients; six patients were used twice, thus making a total of twenty-one observations. Of the fifteen patients, two (nos. 15 and 16) were normal as far as their cardiovascular systems were concerned. Three (nos. 8, 12 and 13) of the remaining thirteen patients suffered from portal cirrhosis and ascites, and nine (nos. 1, 2, 3, 4, 6, 7, 9, 10 and 11) had variable degrees of cardiac decompensation with edema; one patient (no. 5) had anasarca associated with degenerative Bright's disease.

The patients were kept at complete rest in bed throughout the period of observation, including the control periods without medication. When the output of urine remained at a constant level, the bismuth

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1. Hanzlik, P. J.; Bloomfield, A. L.; Stockton, A. B., and Wood, D. A.: Diuresis from Water-Soluble Bismuth, J. A. M. A. **92**:1413 (April 27) 1929. Stockton, A. B.: Proc. Soc. Exper. Biol. & Med. **27**:721, 1930; Arch. internat. de pharmacodyn. et de thérapie **41**:52, 1931.

2. Stockton (footnote 1, third reference).

3. Stockton (footnote 1, second reference).

was injected. A constant intake of fluid and of sodium chloride was maintained throughout. Complete daily twenty-four hour specimens of urine were collected and analyzed. Samples of venous blood were obtained at the same time each day. The urea of the blood and urine was estimated in five patients (nos. 3, 4, 6, 9 and 11), Folin's aeration method being used;[4] the estimations were not extended to the remaining patients because the significance of the changes, for the purpose of the work, was not clear. The chloride of the blood was estimated by Austin and Van Slyke's method,[5] and the chloride of the urine, by the method of Seelman and Volhard,[6] in all but four patients (nos. 1, 5, 7 and 10). The hemoglobin of the blood was estimated in ten patients (nos. 2, 3, 4, 5, 6, 8, 9, 10, 11 and 12), Palmer's method[7] being used. The object of this was to see if changes in the blood volume occurred, but as there were no constant or significant changes demonstrable, the data are omitted. The negative character of these results indicates that the changes in the blood metabolites to be discussed were not the result of changes in the blood volume.

The individual daily changes in the output of water and the chlorides and urea of the blood and urine for the various patients are presented graphically in chart 1. Chart 2 indicates the percentage of change in the different subjects.

In most of the patients, the bismuth was used following the administration of various other diuretics as follows: in patients 3, 7 and 16, after a full course of medication with digitalis; in patients 4, 6, 9 and 10, after digitalis and theophylline; in patient 1, after digitalis, theobromine and theophylline ethylendiamine; in patient 11, after digitalis, theophylline, theobromine sodiosalicylate and mersalyl; in patient 13, after mersalyl and ammonium chloride, and in patient 12, after mersalyl and merbaphen. Only patients 5, 8, 15 and 16 were given bismuth sodium tartrate as the initial diuretic. In other words, the majority, or eleven patients, received the bismuth under unfavorable conditions; that is, after all other medication had failed. In these patients, there was an opportunity for the comparison of bismuth with the more common diuretics. The comparative efficiency of the various diuretics will be considered in a separate paper.

It is seen from the individual data in chart 1 that fourteen of eighteen trials with bismuth in fifteen patients showed a definite diuretic action. Four patients (nos. 4, 10, 12 [second injection] and 13) showed no, or only a slight, increase in diuresis. There was a marked diuresis in ten of the fifteen patients (nos. 2, 3, 5, 6 [first injection], 7, 8, 9,

4. Folin, O.: Ztschr. f. physiol. Chem. **32**:504, 1901.
5. Austin, J. H., and Van Slyke, D. D.: J. Biol. Chem. **40**:345, 1930.
6. Seelman, J. J.: J. Lab. & Clin. Med. **1**:444, 1916.
7. Palmer, W. W.: Proc. Soc. Exper. Biol. & Med. **12**:175, 1914.

11, 12 and 16). Three patients (nos. 6, 7 and 13) showed diuresis after one injection of bismuth, and not after a preceding or subsequent injection. This phenomenon was observed not only with bismuth, but also with the other diuretics. Most patients responded to the first diuretic agent with an increased output of urine, but failed to respond to the second diuretic agent unless an interval of from two to seven days had elapsed between the two administrations. In general, therefore, the usual peculiarities attendant on the actions of diuretics were evident also in the action of bismuth, although the bismuth in the patients here reported acted at a disadvantage in all but four, since it was used only after other diuretics had been tried.

The efficiency of the diuretic action of bismuth, as indicated by the maximum and median percentage changes in the output of urine, is

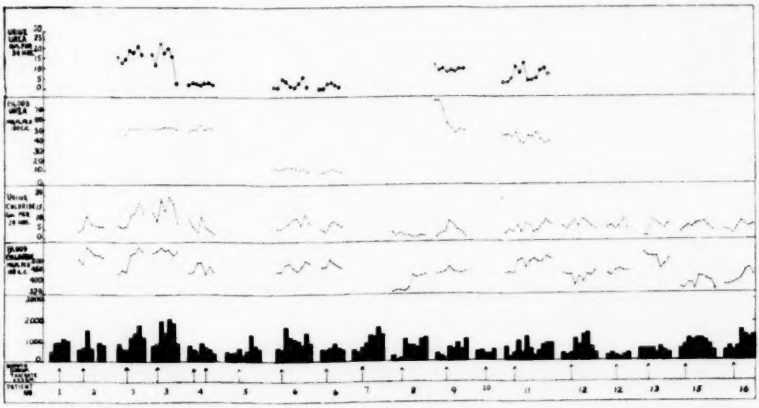

Chart 1.—Diuresis and changes in the chloride and urea of the blood and urine of edematous and normal patients after the intramuscular injection of bismuth sodium tartrate. Each arrow represents a total dose of 0.03 Gm. of the bismuth compound, or 0.022 Gm. of bismuth ion.

shown in chart 2, which also illustrates an attempted correlation with the total fluid removed from the body. The maximum percentage diuresis would indicate the most that might be expected from the bismuth and was obtained by comparing the mean daily output of urine with the peak of daily output after the injection of bismuth. The total fluid removed represented the volume of urine excreted after the administration of bismuth in excess of the mean control level of urine during equal periods of four days.

It is seen that the maximum percentage of diuresis in all patients ranged from minus 18 to plus 360; average, plus 127. The percentage change in the total diuresis as indicated by the difference between the

volume of urine excreted during three days before and three days after the injection of bismuth ranged between minus 48 and plus 228; average, plus 56. Accordingly, both methods of estimating the diuretic efficiency of the bismuth showed a definite and considerable increase in the output of urine. In fact, the data for the percentage of total diuresis testify to the well sustained diuretic action of the bismuth

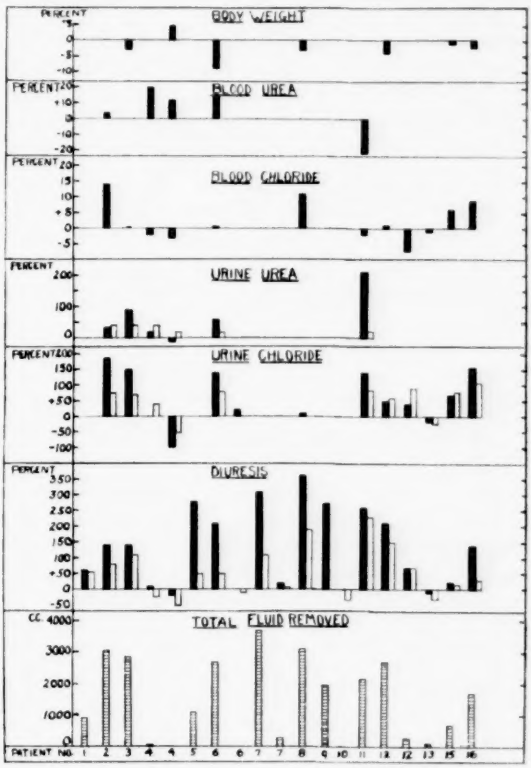

Chart 2.—Total fluid removed and percentage changes in the output of urine, body weight and blood and urine chloride and urea following the injection of bismuth sodium tartrate in edematous patients. The solid blocks represent maximum percentage changes; the hollow blocks, the median change during the four days preceding and the four days following the injection of bismuth.

and the absence of secondary oliguria as compared with merbaphen and mersalyl.[3]

CHANGES IN THE CHLORIDE

Urine.—In eight of the eleven patients studied, the excretion of chloride in the urine increased following the injection of bismuth; the

increase failed only in patients 4, 8 and 13. In patients 4 and 13 the absence of an increase in the excretion of chloride correlated with a failure to respond with an increase in diuresis. In patient 8, the chloride in the urine failed to increase despite a brisk diuresis. On the other hand, patient 6 (second injection), who failed to show an increase in diuresis, and patient 12 (second injection), who showed a doubtful increase, exhibited definite increases in the excretion of urinary chloride amounting to 28.3 and 87.8 per cent, respectively. In seven of eleven patients, there was an increase in the concentration of chloride in the urine independent of the volume of the urine; the concentration of the urinary chloride ranged from minus 70 to plus 70 per cent; average, minus 11 per cent. The variations in the concentrations were too great to indicate their significance, the outstanding item being an absolute daily increase in the urinary chloride.

The percentage changes in the daily excretion of urinary chloride in the urine are shown in chart 2; the changes were plotted in the same way as those for diuresis. It is seen that the maximum excretion of chloride varied from minus 16 to plus 154 per cent; average, plus 67 per cent. The percentage of the total excretion of chloride ranged from minus 50 to plus 110; average, plus 54.7. Thus, the changes in the chloride were in the same general direction as those in the diuresis, but the magnitude of the increases was less, i. e., about one-half. Accordingly, the increase in the output of urine would account for the increased excretion of chloride.

Blood.—The changes in the chloride closely paralleled the changes in diuresis and in urinary chloride, thus pointing to the tissues as the source of extra chloride. An active diuresis following the injection of bismuth was always accompanied by an increase of chloride in the blood, and a decrease or absence of diuresis was accompanied by no change or a decrease of chloride in the blood in three patients (nos. 4, 12 and 13). The changes in the chloride of the blood in the eleven patients observed ranged from minus 7 to plus 14 per cent; average, plus 2.6 per cent.

CHANGES IN THE UREA

Urine.—In six of nine trials with bismuth in the five patients studied, there was a concurrent increase in the excretion of urea with water. One patient (no. 9) showed a decrease, and one patient (no. 4, both trials), no change in excretion. These two patients, who showed no increase of urea in the urine, showed no increase in diuresis. The increases in the average total excretion of urea per day ranged from 14 to 40 per cent; average, 27 per cent; these changes are shown in chart 2. There was also a definite increase in the concentration of urea in the urine of all patients, the daily increases ranging from 5 to 56 per

cent; average, 32 per cent. From these results, it would seem that the increases in the output of urea in the urine were due to the increase in diuresis.

Blood.—The urea in the blood following the use of the bismuth showed no change in six trials in four different patients (nos. 3, 4, 6 and 11) and a decrease in one patient (no. 9). In the latter patient, who had cardiac decompensation, the fall in urea in the blood occurred with the onset of clinical improvement, loss of edema and recovery of the circulation. The urea in the blood of all the patients studied varied from minus 22 to plus 20 per cent; average, plus 5 per cent, all of which testifies to the considerable variation without a significant net change. This might be expected, since the distribution of urea in the body is kept fairly constant, and the balance is not easily upset.

CHANGES IN BODY WEIGHT

In all edematous patients who showed an active diuresis, the loss in body weight was marked. Unfortunately, not all of the patients used could be weighed daily. All of the seven patients who could be weighed lost body fluid following the use of the bismuth, except one (no. 4), in whom diuresis failed to occur. The percentage changes in the body weight in these patients ranged from a gain of 7.4 to a loss of 9.5, the average being a loss of 2.7. The gain in weight occurred in patient 4. The amounts of edema fluid removed during periods of diuresis ranged from 0 to 3,860 cc., an average of 1,448 cc. (chart 2).

COMMENT

Taking the results obtained as a whole, it was found that bismuth sodium tartrate caused diuretic and antiedemic actions in about 73 per cent of the edematous patients observed. The diuresis began in from twenty-four to forty-eight hours after intramuscular injection of the bismuth, and persisted for from two to eight days. The average duration of diuresis was four days, when the output of urine remained at an average of about 56 per cent higher than before the injection of bismuth. The period of maximum diuresis usually fell on the first to the third day following the administration of the bismuth, and at this time the output of urine averaged 122 per cent above the control level. The edema fluid was removed at a slower rate than with other diuretics, such as theophylline, merbaphen and mersalyl, but since the bismuth diuresis continued for several days, the bismuth eventually removed more fluid than the other diuretics.

The most significant changes for the mechanism of the bismuth action were the simultaneous increases in the chlorides of the blood and urine during the increase in diuresis. This correlation is good

evidence in support of a general tissue action of the bismuth, an action in common with that of some other recently studied diuretic agents, namely, theophylline and the organic mercurials, merbaphen and mersalyl. Since the increase in salt of the blood must come from the tissues, the mechanism of the diuretic action, and of the antiedemic action as well, would appear to be essentially a salt action, dependent on a mobilization of the salt in the tissues. Since the increase of chloride in the blood was frequently manifested before the diuretic action, this phenomenon pointed to the tissues as the seat of action of the bismuth. This, however, does not exclude the possibility of the water being removed first from the tissues into the blood. It is possible that both the salt and the water are removed together. Inhibition or paralysis of reabsorption in the renal tubules is not adequate to explain the simultaneous increases in the chloride of the blood and urine. There would seem to be no alternative to some tissue action of the bismuth in order to account adequately for the increased output of sodium chloride in the urine when the chloride in the blood is elevated during the diuresis. These changes in the chloride of the blood and urine of patients agree closely with those in the chloride of the blood and urine of rabbits treated with bismuth.[2]

It has been previously reported, and was constantly observed in the patients of this study, that the chloride in the blood was lower in edematous patients than in normal subjects. This not only would agree with the common view that salt is retained in tissues during edema and account for the low blood salt, but also would point to the tissues as the source of the chloride mobilized by diuretics such as bismuth.

The urea of the body cannot assist satisfactorily in locating the seat of action of diuretics, because any changes in the urea in the blood are quickly adjusted and the concentration is kept constant. The increase in daily urea of the urine might be used as an argument in support of a renal action for the bismuth, i. e., a result indicating inhibition or paralysis of, or injury to, tubular reabsorption. However, a tissue action could not be denied, despite the failure to demonstrate an increase in urea in the blood, which is not practically demonstrable for the reason stated. It is believed that changes in other metabolites that more satisfactorily reflect a direct tissue action should be studied before a general tissue action for various diuretics is finally accepted. Such studies are now being attempted with bismuth. For the present, at least, the chemical evidence points to a tissue action as an important factor in the diuretic action of bismuth and probably also of the organic mercurials and the purines. This evidence does not deny a renal factor in the diuretic action; in fact, the kidney would share the general tissue action. The relative importance of these two factors in the action of diuretics cannot yet be precisely defined.

As for the practical advantages in the choice of bismuth as a diuretic and antiedemic, the following may be stated: Well sustained diuresis, lasting from five to six days, results in the removal of large quantities of fluid; there is an absence of nausea and vomiting, which are frequently caused by theophylline; there is much less danger of metallic poisoning (stomatitis) and renal injury than when merbaphen and mersalyl are used; intramuscular injection avoids the objectionable features of venous injection, which is sometimes resorted to when other diuretics are used, and of oral administration, which, when used for other diuretics, is disturbing to digestion. About the only disadvantage of the use of bismuth is a slower onset of action; bismuth is not as spectacular as are merbaphen and mersalyl. However, this disadvantage is offset by the advantages cited. There is a certain variability in the action of bismuth, but this is also true of all diuretics.

CONCLUSIONS

1. The intramuscular injection of bismuth sodium tartrate into fifteen patients was followed by a definite and sustained increase in diuresis in 73 per cent. The increase in the output of urine correlated with the losses of edema fluid and of body weight in the edematous patients.

2. In the four patients who failed to respond, there was no diuretic action following the use of various other diuretics.

3. In the patients studied, the urea in the blood showed no constant or significant changes, while the urea in the urine generally paralleled the changes in diuresis.

4. The chloride of the blood and urine increased simultaneously during increases in diuresis in the majority, or eight, of the eleven patients studied, thus indicating that the diuretic action of bismuth is mediated through some effect of the metal on the tissues.

5. This correlation of the changes in the chloride of the blood and urine and the diuresis in human subjects agrees with that in rabbits receiving bismuth.[2] The tissue action suggested for bismuth agrees also with that suggested by other investigators for other diuretic agents (merbaphen, mersalyl and theophylline). Various other factors in diuretic actions are discussed.

EXPERIMENTAL LOW COLONIC OBSTRUCTION

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Recent experimental work has emphasized the importance of chloride metabolism in high intestinal obstruction and has offered much of value in the treatment for this condition. Relatively few studies have been made on obstruction low in the large bowel, which produces a somewhat different though not fundamentally dissimilar syndrome. It was felt that a careful study of low obstruction might supplement our knowledge of intestinal obstruction in general by bringing out similarities and differences between low and high obstruction, and might possibly yield information of practical importance for therapy.

McClure,[1] in 1907, produced colonic obstruction by ligation with a cotton cord. Vomiting was prominent, although no food or drink was taken postoperatively. The animals were very drowsy, and the symptoms were progressive; the average length of life was seven days. Dilatation just above the ligature was often enormous, and was uniform up to the ileocecal valve, above which the small intestine gradually tapered to normal size. Brandberg [2] stated that animals with obstruction of the large intestine live longer than those in which the obstruction is in the small intestine; that the cause of death is peritonitis due to gangrene of the colon, and that there are no changes in the blood except those associated with starvation. Wangensteen and Chunn [3] reported that one dog lived forty-two days with complete obstruction low in the descending colon; the blood nonprotein nitrogen in this animal did not increase. Excretion of nitrogen in the urine was increased. At autopsy

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1. McClure, R. D.: An Experimental Study of Intestinal Obstruction, J. A. M. A. **49**:1003 (Sept. 21) 1907.

2. Brandberg, R.: Experimental and Clinical Study of Chemical Blood Changes in Ileus, Acta chir. Scandinav. **65**:415, 1929; abstr., J. A. M. A. **95**:311 (July 26) 1929.

3. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: III. Simple Obstruction: Study of Cause of Death in Mechanical Obstruction of Upper Part of Intestine, Arch. Surg. **16**:1242 (June) 1928.

the entire colon was packed with solid fecal material. Wangensteen stated that the administration of saline solution is of no benefit in such animals.[4]

Several workers [5] have reported on obstruction just above the ileocecal valve, the symptomatology of which is midway between that of high intestinal and that of low colonic obstruction. In such animals vomiting occurs later and is less abundant than is the case in high obstruction; the length of life is longer; the change in the blood chlorides takes place more slowly, and the increase in urea nitrogen is a less prominent part of the picture. In this type of obstruction the subcutaneous administration of sodium chloride is reported to be of some benefit. The picture produced by an obstruction high in the small intestine need hardly be reviewed. It may be recalled, however, that unless chloride is administered death occurs rapidly, with an equally rapid fall in blood chloride and a rise in nonprotein nitrogen. If chloride is given, the animal may be maintained in a fairly normal state for several days.[6]

METHOD

The effects of obstruction of the colon were studied in sixteen dogs, animals dying of pneumonia and perforative peritonitis not being included. In eleven the obstruction was brought about by tying off the descending colon a few inches from the anus with a gauze band. This is a satisfactory method of producing the obstruction, except that the animals must be carefully watched, because they may begin to defecate small amounts after several days. In three of the eleven animals the ligature "slipped" in this way, leaving an opening large enough to admit a small probe. The results in these three animals will be compared with those in the sixteen in which obstruction was complete. In five dogs obstruction was produced by sectioning the descending colon in the same region and inverting the ends with sutures. All surgical procedures were carried out with aseptic technic, pentobarbital sodium or ether being used as the anesthetic.

The plasma chlorides, blood urea, hemoglobin, red cell count, total volume of the blood and blood indican were studied in dogs before and after complete obstruction of the distal descending colon. In addition, several animals received barium enemas just prior to operation, and the position of the barium was observed postoperatively by fluoroscopy and roentgenograms. A careful autopsy was performed in every case.

Plasma chlorides were determined by the method of Rappleye,[7] and blood urea nitrogen was measured by the Folin-Wu technic. The total volume of the blood was determined by the Rountree method, as modified by Hooper, Smith,

4. Wangensteen, O. H.: Minnesota Med. **14**:16, 1931.

5. Haden, R. L., and Orr, T. G.: J. Exper. Med. **37**:365, 1923. Hartwell, J. A.; Hoguet, J. P., and Beekman, F.: An Experimental Study of Intestinal Obstruction, Arch. Int. Med. **13**:701 (May) 1914.

6. Haden, R. L., and Orr, T. G.: Obstruction of the Jejunum; Effect of Sodium Chloride on Chemical Changes in the Blood of the Dog, Arch. Surg. **11**: 859 (Dec.) 1925.

7. Rappleye, W. C.: J. Biol. Chem. **32**:509, 1918.

Belt and Whipple,[8] using vital red. Determinations of blood volume were not repeated more often than every three days, to avoid accumulation of dye in the blood stream. Semiquantitative determinations of blood indican were made by the method of Monias and Shapiro;[9] it was our original intention to perform quantitative studies of blood indican as an index of impairment[9] of the kidney if the findings warranted this, but the only animals in which the blood indican was definitely increased were those in which peritonitis was present as a result of perforation.

RESULTS

In a number of the dogs not included in our series of sixteen, death was due either to pneumonia or to perforation of the large bowel. Perforation usually took place a few inches above the site of obstruction. These dogs were excluded from the series, because we were interested only in the changes produced by simple obstruction of the colon and not in those caused by a complicating peritonitis. In thirteen dogs no cause of death other than the obstruction could be found. The average length of life of these animals was ten and two-tenths days, with a minimum of six and a maximum of twenty-two days. There was no definite difference in the span of life in the dogs in which the obstruction was caused by ligature and those in which the intestine was severed and the ends were inverted. When perforation resulted, it was found to occur at any time from the second to the ninth day. Autopsy observations in the animals dying of simple obstruction were: a greatly dilated large intestine, usually hyperemic on the antimesenteric border but not discolored; a small bowel dilated from one-third to three-fifths of its extent but not hyperemic; a stomach containing considerable amounts of fecal material, and a markedly distended gallbladder. The contents of the small and large bowel were invariably fluid as contrasted with the solid content reported by Wangensteen.[4] The peritoneum was everywhere smooth and glistening, with no excess fluid in the peritoneal cavity.

The animals as a rule ate and drank freely for the first few postoperative days. Water was consumed in moderate amounts by most of the dogs until a few hours prior to death. The appetite gradually decreased, and vomiting of small amounts of material usually began from about the fourth to the sixth day, although the onset of vomiting varied considerably. In the animals that lived longest the vomitus became fecal. Progressive cachexia invariably occurred, and drowsiness was marked; the animals appeared to be dehydrated.

8. Hooper, C. W.; Smith, H. E.; Belt, A. E., and Whipple, G. W.: Am. J. Physiol. **51**:205, 1920.

9. Monias, B. L., and Shapiro, P.: Value of Indican Determination in Blood in Cases of Renal Insufficiency, Arch. Int. Med. **45**:573 (April) 1930.

The plasma chlorides were determined in twelve dogs and the results are summarized in table 1. No significant change in chloride took place even in the dogs that lived nineteen and twenty-two days.

Determinations of the blood urea nitrogen were made in nine animals. All showed a gradual rise. In two instances samples of blood for deter-

TABLE 1.—*Plasma Chlorides After Obstruction*

	Dog											
Day Postoperative	1	2	3	4	5	6	7	8	9	10	11	12
Normal	460	500	525	590	550	560	525	595	552	533	564	565
1	480	510	543	593	...	540	...	...	...	...	...	...
2	478	548	523	...	...	...	572	...	...	...	...	...
3	461	460	520	...	560	...	...	585	498	...	...	...
4	412	533	540	...	...	...	595	595	...	...	...	...
5	338	521	448	598	561	553	556	...	...	...	491	...
6	...	540	485	...	...	...	511	585	445	522	565	...
7	...	...	...	540	500	580	...	...	...	...	...	570
8	...	...	...	...	...	...	523	550	...	...	510	...
9	...	...	...	...	...	...	...	...	...	...	...	...
10	...	...	...	...	...	...	...	540	...	...	519	...
11	...	...	...	...	...	...	535	...	...	...	520	506
12	...	...	...	...	...	...	486	502	...	...	544	...
13	...	...	...	...	...	...	500	585	...	...	...	...
14	...	...	...	...	...	...	520	...	...	...	...	...
15	...	...	...	...	...	...	495	600	...	...	...	...
16	...	...	...	...	...	...	...	...	...	...	...	...
17	...	...	...	...	...	...	500	555	...	...	...	...
18	...	...	...	...	...	...	...	...	...	...	...	...
19	...	...	...	...	...	...	525	582	...	...	...	...
20	...	...	...	...	...	...	531	...	...	...	...	...

TABLE 2.—*Urea Nitrogen After Obstruction*

Day Post-operative	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8	Dog 9
Normal	9.2	12.7	11	12	9.6	9.7	17	13	14.6
1	..	..	..	..	..	..	..	..	..
2	..	..	..	..	..	..	..	..	..
3	..	..	..	13	..	13	..	..	..
4	..	..	..	10	..	..	70	..	..
5	12	20.4	17	..	..	12.5	..	24	18
6	..	21.6	..	16.4	14	..	..	..	..
7	19.8	..	..	..	..	18.1	..	..	..
8	..	22.5	65	..	..	21	..	..	..
9	..	..	..	..	..	..	..	..	..
10	..	22	..	..	..	..	..	..	..
11	12	..	..	..	..	..	..	..	..
12	14.7	22	..	..	..	..	..	..	..
13	14.3	..	..	..	..	..	..	..	..
14	14	23	..	..	..	..	..	..	..
15	18.3	29	..	..	..	..	..	..	..
16	..	32	..	..	..	..	..	..	..
17	24.3	35	..	..	..	..	..	..	..
18	..	45	..	..	..	..	..	..	..
19	28.6	..	..	..	..	..	..	..	..
20	28.8	..	..	..	..	..	..	..	..

mination of urea were drawn from the heart a few minutes prior to death; these determinations gave sixty-five and seventy mg. of urea nitrogen, respectively, per hundred cubic centimeters. In both of these animals there was no cause for death other than the obstruction. These results are shown in detail in table 2.

Red blood cell counts, hemoglobin and determinations of blood volume were made on six animals. The red blood cell count and hemo-

globin showed little change. In four of the six dogs, however, the blood volume definitely decreased. The figures are given in table 3. The changes in blood volume are strikingly illustrated by dog 5, which began to defecate small amounts on the seventh day; in this animal the blood volume first decreased thirty-eight per cent, and then, after the obstruction was partly relieved, it rose above its normal level.

Semiquantitative tests for blood indican were made on eight dogs. The amount of indican increased very slightly above the level shown by normal controls; according to Monias and Shapiro,[9] the maximum amount present was not sufficient to indicate impairment of the kidneys.

Although the fecal vomiting observed would seem to indicate regurgitation from the lower part of the bowel, it seemed important to show

TABLE 3.—*Hemoglobin, Red Blood Cell Count and Blood Volume After Obstruction*

Number of Dog	Day Post Operation	Hemoglobin, per Cent	Red Blood Cell Count	Length of Life, Days	Blood Volume, Cc.	Comment
1	Normal	110	7,440,000	..	1,660	
	4	120	8,640,000	6	1,770	
2*	Normal	100	6,350,000	..	1,469	
	3	100	6,400,000	5	1,344	
3	Normal	101	6,750,000	..	1,632	
	3	103	6,320,000	..	1,397	
	7	105	6,810,000	..	1,289	
	11	95	6,720,000	12	1,069	
4	Normal	102	7,660,000	..	1,131	Ligature slipped on seventh day
	5	106	6,920,000	..	697	
	8	102	7,330,000	..	1,456	
5	Normal	95	6,650,000	..	1,681	
	4	97	7,170,000	6	1,007	
6	Normal	104	7,550,000	..	1,495	
	4	105	7,830,000	8	992	

* This dog died of peritonitis secondary to perforation two days after the second determination of blood volume.

conclusively that this occurred because passage of colonic contents to the small intestine, where they might be more readily absorbed, could be a factor in the production to toxemia. The fecal character of the vomitus could result from the extension of colonic flora into the gastrointestinal tract. Fluoroscopy and roentgenograms showed that barium placed in the colon by enema before operation gradually moved up into the small intestine. Barium was not observed to reach the stomach, probably because dilution by fluid in the upper part of the small intestine reduced the concentration of barium to a point where no shadow was cast. In a preliminary report [10] we stated that the barium placed in the colon was not seen to pass back past the ileocecal valve. At

10. Roberts, G. M., and Crandall, L. A., Jr.: Proc. Soc. Exper. Biol. & Med. **28**:942, 1931.

this time we were following the position of the barium by fluoroscopy only; more recently roentgenograms have shown definitely that the barium is regurgitated into the small bowel.

It is interesting to compare the results in the dogs in which the obstruction was relieved by loosening of the ligature with those in the animals in which the intestinal closure was permanent. The return to a normal blood volume in dog 4 (table 3) has already been noted. In the other two animals in which this occurred only the plasma chloride was determined; in two dogs the chlorides showed a tendency to fall, even though the animals passed small amounts of liquid feces and their general condition improved. It was striking to see the change from a listless state to more nearly normal vigor in these animals after the passage of small amounts per rectum for a few days. Two dogs with an intentional partial obstruction were observed by one of us (Dr. Crandall), although chemical examination of the blood was not made. These animals lost weight, but showed almost normal spontaneous activity. Death occurred after four and five weeks, and was due to a complete obstruction caused by a mat of hair and feces lodged at the site of ligation. Intestinal distention in these animals was enormous.

COMMENT

It is to be noted that while the period of survival of some of our animals approached that of animals subjected to simple starvation, the majority died in from six to twelve days. Loss of chlorides is evidently a factor of slight, if any, importance; changes in chloride metabolism are further eliminated by the observation of Wangensteen and Chunn [3] that administration of chlorides is of no benefit in these animals. The picture presented is that of toxemia. The obvious factors to be considered are dehydration, injury to the kidney and absorption of some unknown toxin from the bowel.

The presence of renal damage might be inferred from the rise in blood urea nitrogen, but the slight change in blood indican contradicts such a supposition. The situation is in all probability similar to that occurring in high obstruction, in which the increase in blood urea nitrogen is not accompanied by an increase in the other fractions of the nonprotein nitrogen. Several workers have indicated that while some renal impairment is present in high obstruction, it is probably not sufficient to account for the death of the animals.[11]

The dehydration that occurs is severe. Three of our animals lost 30, 40 and 33 per cent of their blood volume respectively, these losses

11. Cooper, H. S. F.: Cause of Death in High Obstruction, Arch. Surg. **17**: 918 (Dec.) 1928. McQuarrie, I. and Whipple, G. H.: J. Exper. Med. **29**:397, 1919.

being present one, two and four days before death. A fourth animal lost 38 per cent of its blood volume, but then began to defecate small amounts and recovered. Of the remaining two dogs, one had lost about 8 per cent of the blood volume and the other showed an increase of 7 per cent, readings in both cases being made two days before death. Owing to technical difficulties in making repeated determinations, we have not been able to determine the blood volume at as short intervals as would be desirable, and we realize that the dehydration may be sufficient in the last hours of life to be of itself a cause of death. The cause of the dehydration is obscure. No large amounts of fluid were lost by vomiting in any case, nor was the amount in the bowel large enough to account for the loss of fluid when it is considered that the animals took water by mouth voluntarily up to a short time before death. The relative constancy of the red cell count and the determinations of hemoglobin in the face of the decreasing blood volume show that the former factors cannot be relied on to give an index of blood concentration. The findings can be interpreted only as a storage or a destruction of red cells.

We believe that our studies indicate that in low obstruction some toxic material is absorbed from the intestine which is responsible for the fatal issue. We have no crucial evidence to present on this point; such a deduction is purely a matter of elimination. The toxic substance must also be responsible for the decrease in the blood volume. Those who have studied high obstruction are divided in opinion, some believing that the sole cause of death is the loss of fluid and salts,[12] others presenting evidence that a distended mucosa may absorb such toxic substances.[13] In low obstruction the issue seems somewhat clarified; there is no rapid loss of chloride to obscure the picture, and there is no extremely rapid piling up of nonprotein nitrogen. For the first few days the animals appear essentially normal. It may well be that symptoms from such an obstruction do not begin to appear until the entire colon is distended to its maximum capacity and material begins to accumulate in the lower part of the small bowel. Dragstedt, Lang and Millet[14] have presented reasons for believing that the colon is less

12. White, J. C., and Fender, F. A.: Cause of Death in Uncomplicated High Intestinal Obstruction, Arch. Surg. **20**:897 (June) 1930. Gamble, J. L., and Ross, S. G.: J. Clin. Investigation **1**:403, 1925.

13. Dragstedt, L. R.: Proc. Soc. Exper. Biol. & Med. **25**:239, 1928. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: J. Exper. Med. **30**:109, 1919.

14. Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: Relative Effects of Distention on Different Portions of the Intestine, Arch. Surg. **18**:2257 (June) 1929.

susceptible to injury by distention than is the ileum, and the ileum less than the jejunum. We suggest that the immediate relief that follows even the smallest opening at the point of obstruction is an additional reason for believing that the primary factor is distention with an attendant change in the permeability of the intestinal mucosa.

CONCLUSIONS

1. In a series of animals subjected to two types of surgical obstruction of the descending colon, thirteen died from no apparent cause other than the obstruction. The average length of life was ten and two-tenths days, the maximum being twenty-two and the minimum six.

2. Such animals show no significant change in plasma chlorides at any time.

3. The blood urea nitrogen increases gradually, and in our series reached a maximum value of 70 mg. per hundred cubic centimeters at the time of death.

4. A slight increase in blood indican was observed.

5. The red blood cell count and the hemoglobin show no definite change. There is a tendency for the blood volume to decrease sharply, the maximum loss observed being 40 per cent.

6. Regurgitation of barium from the colon into the small intestine has been demonstrated in these animals.

7. The possible causes of death are discussed.

TOXICITY OF MERSALYL (SALYRGAN)

A CLINICAL AND ANATOMIC STUDY

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Despite the widespread use of the newer mercurial diuretics, merbaphen (novasurol) and mersalyl (salyrgan), there still exists some doubt as to their ultimate harmlessness. Stomatitis, colitis, proctitis, purpura, hematuria and even death have been reported following the use of novasurol. With the introduction of salyrgan there was noted a decrease in the severity and number of the reactions.[1]

In his experiences with both drugs, Petzal [2] called attention to the change. In several hundred injections of salyrgan he saw no toxic manifestations. At necropsy Agnew [3] observed hemorrhagic colitis in eight subjects following the use of novasurol, but no such manifestation occurred after the injection of salyrgan, despite its more extensive use at that time (1926). Bernheim [4] recorded the administration of 1,000 injections of salyrgan without complicating reactions. Tschernning [5] warned against the active use of the drug in aged men with complicating prostatic hypertrophy. In four of his patients there was a

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1. Zeiler, K.: Novasurol, ein neues Quecksilbersalz zur Syphylisbehandlung, mit Bemerkungen ueber die Grundsaetze der Quecksilberbehandlung, München. med. Wchnschr. **44**:1257, 1917. Christian, H. A.: Diuretics—Their Utility and Their Limitations, Boston M. & S. J. **197**:614, 1927. Snell, A. M., and Rowntree, L. G.: Purpuric Skin Manifestations Following the Use of Merbaphen, Ann. Int. Med. **2**:97, 1928. Redlich, F.: Letale Quecksilber Intoxication nach einmaliges Novasurol Injektion, Wien. klin. Wchnschr. **38**:359, 1925. Gunsberg, M.: Klinische Erfahrungen ueber Salyrgan, ein neues Diuretikum, Deutsche med. Wchnschr. **51**:604, 1925. Marvin, H. M.: Merbaphen as a Diuretic in Congestive Heart Failure, J. A. M. A. **87**:1016 (Sept. 25) 1926. Sprunt, D. H.: Renal Damage Following Administration of Merbaphen, Arch. Int. Med. **46**:494 (Sept.) 1930.

2. Petzal: Erfahrungen mit Salyrgan, Deutsche med. Wchnschr. **52**:1651, 1926.

3. Agnew, G. H.: Salyrgan as a Diuretic, Canad. M. A. J. **18**:45, 1928.

4. Bernheim, E.: Ueber das neue Quecksilberpräparat, Salyrgan, als Diuretikum, Therap. d. Gegenw. **65**:538, 1924.

5. Tscherning, R.: Ueber Salyrgan, Deutsche med. Wchnschr. **53**:1465, 1927.

profuse diuresis followed by acute retention owing, probably, to prostatic swelling. Petri [6] recorded changes in the colon consisting of greenish-yellow, sparsely placed, superficial ulcerations which appeared after effective injections of novasurol and salyrgan.

Grossman,[7] reviewing his experience with nearly 10,000 injections of salyrgan, recalls no damage that he could directly attribute to the drug. Because the chemical structure of salyrgan is different from that of novasurol, he believes that its toxicity is not the same. He cites the history of two patients suffering from congestive heart failure with generalized edema and ascites, in whom the injection of from 0.5 to 1 cc. of novasurol produced diuresis accompanied by hemorrhagic stomatitis and colitis. Salyrgan was equally effective as a diuretic but caused no complications. Grossman was able to continue the administration of the latter drug for months at a time, giving as many as three injections per week. Fishberg [8] speaks of the replacement of novasurol by salyrgan in the use of mercurial diuretics in the treatment of edema.

In a recent review of mercurial diuretics, Engel and Epstein [9] reported their own experience with several thousand injections of salyrgan. They regard the use of novasurol as obsolete. They can replace it with salyrgan and produce an equally effective diuresis, and they seldom see any complications due to mercurial intoxication.

During the past five years at the Montefiore Hospital when a mercurial diuretic was found necessary, only salyrgan was used. In more than 3,000 injections given to date, there have been only isolated instances of harmful reactions. To complete the clinical impression of the lesser toxicity of salyrgan as compared with other mercurial diuretics we have attempted a correlative study of the course of illness, the amount of drug administered and the anatomic findings in a group of thirty patients who were followed at the hospital for the past five years. They were as a rule patients with signs of severe congestive heart failure, who had been admitted to other institutions several times previously. They were observed and treated at the hospital until death. In all cases special search was made for signs of mercurialism in the kidney. The colon was investigated only in the gross, and in no case were signs of ulceration found.

6. Petri, E., Vergiftungen, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927.

7. Grossman, M.: Moderne Diuretika, Schweiz. med. Wchnschr. **58**:1249, 1928; Novasurol und Salyrgan, Med. Klin. **21**:1730, 1925.

8. Fishberg, A.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930, p. 101.

9. Engel, K., and Epstein, I.: Die Quecksilberdiurese, Ergebn. d. inn. Med. u. Kinderh. **40**:187, 1931.

From a clinical point of view our patients showed only a negligible number of reactions attributable to mercury itself. In one patient a wrist-drop developed and two had foot-drop incidental to faulty intramuscular injections. In two patients with impaired renal function a mild stomatitis developed following a single injection of salyrgan.

Since the toxic action of mercury is both immediate and remote, we have included in our reports a group of patients to whom the salyrgan was given shortly before death, although the amount administered was small. Salyrgan was withheld only in those who showed severe renal damage, such as elevated amount of urea in the blood, hematuria, or a low fixed specific gravity of the urine. Albuminuria and casts were not contraindications. The total amounts of salyrgan given ranged from 4 to 130 cc.

Of all the patients investigated only one showed a renal lesion suggestive of mercurial intoxication. The protocol of the case follows.

REPORT OF A CASE

History.—C. C., a pale Italian boy of 5 years, was admitted to the hospital on July 23, 1928, with a history referable to chronic rheumatic cardiovalvular disease for the past year. Throughout this period he showed slight rises in temperature, which might be interpreted as signs of rheumatic activity. When first seen he was acutely ill, with intense dyspnea and orthopnea. Cyanosis of the lips, ears and fingers was present. The veins of the neck were distended. The heart was markedly enlarged to the left and the right, with the apex beat 8 cm. to the left of the midsternal line and in the fifth interspace. The liver was palpable two fingers below the costal margin. There was no evidence of edema or ascites.

Course.—During the first month the patient was afebrile, and after a short period of rest the dyspnea diminished, leaving him much more comfortable. On Aug. 26, 1928, acute pharyngitis with a rise in temperature to 104 F. developed. This lasted two days and the temperature then returned to normal. On September 13, nearly two weeks later, edema of the lower extremities and puffiness of the face were noted. The patient was intensely dyspneic as well. Following the administration of 4 cc. of tincture of digitalis per rectum there was a striking but temporary improvement. For the next three weeks there was a marked edema of the scrotum and penis, with edema of the lower extremities and fluid in the abdominal cavity. Tincture of digitalis, urea and salyrgan were of no avail in the treatment of this fluid accumulation. Salyrgan was administered as follows: On October 16, 1 cc. was given; October 19, 0.5 cc.; October 22, 0.5 cc.; October 29, 0.5 cc.; November 3, 0.5 cc., and November 5, 1 cc. The patient expired on November 7, of cardiac insufficiency.

Laboratory Data.—Urinalysis showed a specific gravity of from 1.019 to 1.026 and negative results for albumin and casts. The total daily volume of urine without salyrgan ranged from 125 to 400 cc.; with salyrgan as much as 860 cc. was collected. The collection of urine was not possible after the development of edema of the penis and scrotum.

Examination of the blood made on July 25 showed 16 mg. of urea nitrogen per hundred cubic centimeters, a negative Wassermann reaction and 80 per cent of hemoglobin.

Roentgen examination of the chest showed moderate pulmonary congestion, a globular heart with a rounded and prominent left ventricle and pulmonary conus. On fluoroscopic examination the left auricle was seen to bulge into the retrocardiac space. An electrocardiogram showed deviation of the left axis.

Autopsy.—Autopsy was performed seven hours after death. The incision was limited to the chest. The body was that of a well nourished boy, 103 cm. long. There was marked edema of the feet and genitalia. The glans penis felt almost cystic.

The anatomic diagnosis was chronic rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency, cardiac hypertrophy and dilatation, chronic passive congestion of the viscera and mercurial nephritis (?). Only the positive observations are recorded.

The lungs were normal, except for numerous subpleural, petechial hemorrhages. The heart showed dilatation and hypertrophy, especially of the right ventricle. The mitral valve was slightly thickened at the edges. The aortic cusp had a few vegetations along the line of closure. The chordae tendineae were shortened and thickened. The posterior cusp of the aortic valve was also slightly thickened. The spleen was the seat of chronic passive congestion. The liver was large and soft and weighed 600 Gm. On section the lobules were well marked. The entire parenchyma was remarkably fatty and light.

The kidneys weighed 80 Gm. each and measured 8½ by 4 by 3 cm. Both were somewhat flabby. On section the parenchyma was pale olive brown. The cortex was demarcated from the medulla by its bloodless appearance and lighter color. The pyramids were well defined. Some of them were slightly injected. Cortical rays, though perceptible with difficulty, were regular in arrangement. The pelvic mucosa was pale and smooth. The ureters showed no abnormalities.

The esophagus, stomach, colon and appendix showed no abnormalities. There were a few small petechial hemorrhages at the jejuno-ileal junction.

Microscopically, the salient observations aside from those in the kidneys were areas of fibrosis in the cardiac muscle and fatty degeneration in the liver with increase in the periportal fibrous tissue.

The kidneys showed a striking anemia of the glomeruli, though the rest of the organ exhibited evidence of chronic passive congestion. The capillary tufts were fairly large. There was no evidence of proliferation of the epithelial elements. The tubules showed an irregular distribution, with from a moderate to a severe degree of cloudy swelling. Many were filled with granular débris, and occasionally contained clumps of red blood cells. In some of the convoluted tubules small foci of calcification were present within the tubular epithelium; small calcific masses were occasionally found in the lumina of the tubules as well.

There was marked congestion of the capillaries of the interstitial tissue in contrast to the ischemia of the glomeruli. The blood vessels showed no abnormalities. The contrast of ischemic glomeruli in an organ otherwise the seat of passive congestion was consistent with a severe interference in glomerular function.

While experimentally in animals the criteria and diagnosis of mild hydrargyrism may readily be established, they are less clearly defined in human beings suffering from antecedent disease of the kidney. Harmon [10] has shown that the lesions of mercuric chloride poisoning

10. Harmon, E. L.: Human Mercuric Chloride Poisoning by Intravenous Injection, Am. J. Path. **4**:321, 1928.

in man are the same whether the drug is administered by the parenteral or the oral route. The salyrgan was administered both intramuscularly and intravenously. Difficulties are to be expected when one seeks the finer anatomic criteria of hydrargyrism in the kidneys of patients who have suffered from a long, debilitating illness, with chronic passive congestion of the viscera, or from a terminal acute infection. In the groups of older patients the presence of arteriosclerotic and arteriolosclerotic lesions with varying grades of destruction of the renal parenchyma made it difficult to determine the presence of changes specifically associated with mild mercurialism.

With these considerations in view, it was felt that only in the presence of a severe necrosis of the tubular epithelium or the characteristic calcium deposits, or both, was a diagnosis of mercurial poisoning justifiable on anatomic grounds.

As the accompanying table shows, these signs of hydrargyrism in the kidneys studied were absent, with one possible exception. Such changes as were found are to be explained by the concomitant arteriosclerosis and arteriolosclerosis, by the terminal acute infection or by the chronic passive congestion. While it is true that cloudy swelling of the tubular epithelium occasionally presents itself in the absence of a diagnosis of pneumonia or other acute infection, it must be borne in mind that chronic passive congestion itself is sufficient to produce such a change.

The case reported, case 3, looks suspicious, in view of the remarkable anemia of the cortices of the kidney in an otherwise deeply congested cadaver. Furthermore, there were slight but definite deposits of calcium in the tubular epithelium and lumina. The tubular epithelium itself exhibited more than the usual amount of cloudy swelling, which amounted at times to a granular débris that filled the lumina, in the absence of an acute terminal infection. The clinical history warranted the use of strenuous measures in this case. The fact that the patient was a 5 year old child is not significant, since we have administered the drug repeatedly to children with severe congestive heart failure and no complications have ensued.

It is most remarkable that, despite the severe degenerative lesions present in many of the hearts and kidneys of our autopsy material, the patients were not injured by the repeated injection of salyrgan. In one patient the amount injected was 130 cc. In a few instances the colonic mucosa was congested and edematous. Severer lesions were not observed.

Conclusions as to the toxicity of the mercurial diuretics based on animal experimentation must be applied with caution to man. John-

stone and Keith [11] found 0.05 cc. of novasurol per kilogram toxic for rabbits if given repeatedly. Death was the result of a variable grade of nephritis. The impression that salyrgan in similar doses is less dangerous is not borne out by Möller.[12] He found that 0.04 cc. per kilogram of the drug did not produce diuresis in rabbits, but resulted in albuminuria, while when 0.06 cc. was given there were diuresis, albuminuria, red blood cells and casts in the urine. Pathologically, he found that renal damage could be demonstrated as early as four and a half hours after the injection. Repeated injection with this same dose at ten-day intervals resulted in chronic nephritis. In dogs, however, Möller found no evidence of renal irritation with as much as 0.06 cc. of salyrgan per kilogram. He distinguishes the response in the rabbit from that in the dog, and believes that man approximates the latter in his behavior to the drug.

Fourneau and Melville [13] studied the pharmacologic action of eighteen separate mercurial preparations having diuretic properties. Depending on their chemical structure, these preparations could be divided into several groups. While the effect of the injection of salyrgan was not specifically observed, it is sufficiently close in structure to neptal, one of the drugs investigated, to allow one to apply the same conclusions. They found that the intake of fluid is an important factor in the determination of the toxic dose of mercurial diuretics in the rabbit and probably in other animals. The same doses were no longer fatal when 200 cc. of distilled water was administered by stomach tube either shortly before or after the injection of the drug tested. According to them, the minimum toxic dose is that weight of the drug which when injected intravenously into an animal kept on a basal, water-free diet, leads to progressive emaciation and death of the animal in from seven to fourteen days after the injection. They found a toxicity for the separate groups which is fairly uniform for the individual members. It seems to be part of the chemical structure.

The different standard of toxicity employed by Fourneau and Melville yielded absolute values for the toxic doses of novasurol and salyrgan about three times those of previous investigators. Yet they too found the novasurol group less toxic than the salyrgan for the rabbit. These results are contrary to the general impression received by the clinical investigators cited previously and serve to illustrate the difficulty of transferring dosages from one species to another.

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11. Johnstone, B. I., and Keith, N. M.: Toxicity of Novasurol, Arch. Int. Med. **42**:189 (Aug.) 1928.

12. Möller, K. O.: Untersuchung ueber die Pharmakologie des Salyrgans. I, II, III, Arch. f. exper. Path. u. Pharmakol. **148**:56, 67 and 81, 1930.

13. Fourneau, E., and Melville, K. I.: Studies in Mercurial Chemotherapy. I, II, J. Pharmacol. & Exper. Therap. **41**:21, 1931.

No.	Case No.	Age	Period of Observation, Mo.	Salyrgan Dosage	Total Salyrgan, Cc.	Chief Anatomic Diagnosis at Autopsy	Comment on Kidney
1	18233	13	1	3 injections of 1 cc. each two weeks before death	3	C.R.C.V.D.,* acute rheumatic myocarditis, C.P.C.* of viscera	Congestion of glomeruli and capillaries; rest of kidney appeared normal
2	15911	54	62	2 doses in last 5 days of life	4	Right heart failure secondary to long standing asthma and emphysema, bronchiectasis, C.P.C. viscera	Diffuse arteriolosclerosis with replacement fibrosis of moderate number of glomeruli, congestion throughout
3	16607	5	4	6 injections in last 3 weeks	4	C.R.C.V.D., see report of case	See report of case
4	16659	12	24	4 injections in last month of life	4	C.R.C.V.D., fibrinopurulent pericarditis, multiple old infarcts in the lungs, C.P.C. of viscera	Marked congestion of medulla and cortex, with cloudy swelling of tubular epithelium
5	17041	53	1	3 injections in last 3 weeks of life	5	Syphilitic aortitis with destruction of aortic cusps, anasarca	Arteriosclerosis and arteriolosclerosis with marked congestion of parenchyma
6	17167	54	10	3 injections in last 2 weeks of life	6	Chronic pulmonary emphysema, cardiac hypertrophy and dilatation, C.P.C. of viscera, bronchopneumonia	Areas of anemic infarction in left kidney, moderate arteriolosclerosis
7	17947	11	8	4 injections of 1 cc. each 3 months before death, 2 cc. in last 2 weeks	6	C.R.C.V.D., bronchopneumonia, C.P.C. of viscera	Moderate congestion, granular degeneration of tubular epithelium
8	16855	61	2	4 injections in last 2 weeks of life	7	C.R.C.V.D., bronchopneumonia, C.P.C. of viscera	Arteriolosclerosis with replacement fibrosis of many glomeruli, congestion, granular degeneration of tubular epithelium
9	14329R	65	53	4 injections in last month of life	8	C.R.C.V.D., C.P.C. of all viscera	Diffuse arteriolosclerosis with replacement fibrosis of many glomeruli
10	17919	54	2	4 injections including one on day of death	8	Coronary occlusion with myocardial infarction, serofibrinous pleurisy	Arteriolosclerosis, moderate congestion, granular degeneration of tubules
11	15361R	39	5	6 injections, 4 in last month of life	12	C.R.C.V.D., C.P.C. of viscera	Thrombosis of right renal vein, old and fresh infarcts throughout kidneys, widespread destruction of renal parenchyma
12	16533	34	3	Numerous injections before admission, 6 during stay	12+	C.R.C.V.D., C.P.C. of viscera, adherent pericardium	Extreme congestion, granular degeneration of tubules
13	17368	68	3	6 injections in last 3 weeks of life	12	Coronary occlusion, myocardial fibrosis, acute pericarditis, C.P.C. of viscera	Arteriosclerosis and arteriolosclerosis, marked fragmentation and vacuolization of tubular epithelium
14	19464	64	10	6 injections in last 7 weeks of life, 1 on day before exitus	12	Hypertensive heart disease, coronary occlusion, C.P.C. of viscera	Diffuse arteriolosclerosis, replacement fibrosis, congestion

15	14555R	60	25	Occasional dose at start, 4 injections in last 2 months	14	Sclerosis of coronary arteries, myocardial fibrosis, anasarca	Diffuse arteriolosclerosis with replacement fibrosis
16	14945	26	12	7 injections in last 3 months of life	14	C.R.C.V.D., C.P.C. of viscera	New and old infarcts in both kidneys, granular and fatty degeneration of tubules
17	16900	59	9	4 injections at start, 3 in the last month of life	14	Syphilitic aortitis generalized arteriosclerosis, C.P.C. of viscera	Arteriolosclerosis, moderate congestion, old and recent areas of infarction
18	19497	63	29	Numerous injections before admission, 8 in last 8 weeks of life	16+	Coronary artery disease, C.P.C. of viscera	Arteriolosclerosis, replacement fibrosis, congestion
19	14635R	62	10	10 injections in last 5 months of life	20	Cardiac hypertrophy and dilatation, C.P.C. of viscera, bronchopneumonia	Arteriolosclerosis, congestion, granular degeneration of tubular epithelium
20	19294	56	6	Several injections before admission, 10 during stay	20+	Coronary sclerosis and occlusion, myocardial infarction, C.P.C. of viscera	Marked congestion, diffuse arteriolosclerosis with replacement fibrosis
21	16283	57	12	14 injections throughout stay	28	C.R.C.V.D., thrombosis of right pulmonary artery, C.P.C. of viscera	Diffuse arteriolosclerosis with replacement fibrosis, moderate congestion
22	12554	30	22	18 injections in last 6 months of life	31	C.R.C.V.D., pulmonary infarction, C.P.C. of viscera	Marked congestion, healed infarcts, granular degeneration of tubules
23	16372R	63	12	18 injections in last 5 months of life	35	C.R.C.V.D., carcinoma of the lung, C.P.C. of viscera	Diffuse arteriolosclerosis with replacement fibrosis
24	19192	49	34	30 injections during stay; wrist-drop developed after intramuscular injection	60	Cardiac hypertrophy and dilatation, C.P.C. of viscera	Diffuse arteriolosclerosis, congestion, granular degeneration of tubules
25	17095	46	7	37 injections during hospital stay	74	Cardiac hypertrophy and dilatation, C.P.C. of viscera, bronchopneumonia	Arteriosclerosis and arteriolosclerosis with replacement fibrosis, congestion
26	16270R	60	20	38 injections during hospital stay	76	C.R.C.V.D., coronary occlusion, C.P.C. of all viscera	Diffuse arteriolosclerosis with replacement fibrosis, marked congestion
27	18291	24	30	Numerous injections before admission, 43 during stay	86+	C.R.C.V.D., C.P.C. of viscera	Intense congestion so marked that glomeruli appear swollen
28	19220	39	12	Frequent injections before admission, 48 during hospital stay	96+	Cardiac hypertrophy and dilatation, C.P.C. of viscera	Diffuse arteriolosclerosis, replacement fibrosis, granular degeneration of tubular epithelium
29	14301R	36	22	Numerous injections before admission, 54 during hospital stay	108+	C.R.C.V.D., C.P.C. of viscera, bronchopneumonia	Diffuse arteriolosclerosis with replacement fibrosis
30	19773	54	12	65 injections during hospital stay, many others before admission	139+	Coronary artery disease with old and recent occlusions, C.P.C. of all viscera	Diffuse arteriolosclerosis with replacement fibrosis, marked congestion

* C.R.C.V.D. means chronic rheumatic cardiovalvular disease, and C.P.C., chronic passive congestion.

Salyrgan is dispensed in a 10 per cent aqueous solution, each cubic centimeter of which contains about 40 mg. of mercury.[14] Though it is apparently harmless on the basis of the mercurial content, it must be borne in mind that nearly 80 per cent of the mercury is excreted in the urine within twenty-four hours.[12] While the usual dose is 2 cc. every two to three days, single doses of 4 and 5 cc. have been injected without ill effect.[9] When the diuretic response is absent after the injection of 2 cc. of salyrgan, it would be a much safer and more effective procedure to resort to the adjuvant therapy of the acid-producing salts rather than to larger doses of salyrgan. Important as well is the fluid content of the body. The edema may act as a protective device against the mercurial intoxication, even as excess amounts of water spare the rabbit [13] and the dog [15] suffering from mercury poisoning.

SUMMARY

1. The comparative toxicity of salyrgan and novasurol is reviewed from the clinical and experimental results reported in the literature.

2. The inconsistency between the clinical findings and the results of animal experimentation is noted.

3. In more than 3,000 injections of salyrgan given at the Montefiore Hospital only two instances of mild stomatitis were encountered when the drug was administered to patients with impaired renal function. In one patient wrist-drop developed and in two foot-drop following faulty intramuscular injection.

4. Anatomic studies were made of thirty patients with congestive heart failure who were given repeated injections with doses of salyrgan up to 130 cc.

5. In one case a lesion suggestive of mercurialism was found at autopsy in the kidney.

14. Collins, G. W.: Chemical Examination of Salyrgan, J. A. M. A. **91**:1994 (Dec. 22) 1928.

15. Haskell, C. C.; Carder, J. R., and Coffindaffer, R. S.: The Value of Forcing Fluids in the Treatment of Mercuric Chloride Poisoning, J. A. M. A. **81**:448 (Aug. 11) 1923.

Book Reviews

History of Medicine in the United States. By Francis R. Packard. Price, $12. Pp. 1323. New York: Paul B. Hoeber, Inc., 1931.

This book is a successor to Packard's well known "History of Medicine in the United States," which has long been out of print. The first volume is in the form, for the most part, of a narrative history of medicine in the United States, but the second volume contains a series of articles on the history of various aspects of medicine to present times. The book is to be judged, therefore, rather as a treasure of information on the history of American medicine than as a consecutive account. Its scope is best shown by its table of contents:

Volume I

I. Medical Events Connected with the Early History of the English Colonies in America.
II. Epidemic Sickness and Mortality in the English Colonies in North America from Its Earliest Discovery to the Year 1800.
III. Early Medical Legislation.
IV. The Earliest Hospitals.
V. Medical Education Before the Foundation of Medical Schools.
VI. The Earliest Medical Schools.
VII. Pre-Revolutionary Medical Publications.
VIII. The Medical Profession in the War for Independence.
IX. The Medical Department of the Army from the Close of the Revolution to the Close of the Spanish-American War.

Volume II

X. History of the Medical Department of the United States Navy.
XI. Some of the Medical Schools Founded During the First Half of the Nineteenth Century.
XII. Outlines of the Development of Medical Practice and Education in Some of the States.
XIII. Foreign Influences on American Medicine.
XIV. Some Notable Events in American Medicine and Surgery.

Appendixes

A. The Examination of Dr. Church.
B. Clinical Lecture Delivered by Dr. Thomas Bond Before the Managers of the Pennsylvania Hospital on Nov. 26, 1766.
C. Surgeon Generals of the United States Army from the Organization of the Medical Department in 1818 to 1931.
D. The Humane Society of Philadelphia.
E. The Ether Controversy.
F. Items of Information on the Organization of Medical Education Compiled from Various Sources.
G. American Journal of the Medical Sciences.
H. The Boston Medical and Surgical Journal.
I. Some Homeopathic Medical Colleges.
J. Women in Medicine.
K. The Botanic, Physio-Medical and Eclectic Schools of Medicine in the United States.

The volumes contain a vast collection of information, and a laborious and useful work has been done in their preparation. Few facts in the history of

American medicine to recent days have been omitted. In the second volume there is a good deal of inequality, and there are some inaccuracies, owing to the material with which the author has had to deal. The history of American medicine has been recorded much less carefully and completely in some parts of the country than in others. But, as the author says, "If I were to have waited to acquire the material for a complete history of medicine in the United States down to any selected date, let us say even as early as 1850, I would never have been able to fulfil my purpose, which is to present to those interested as much material bearing on the history of medicine in America as I could collect, in the fond hope that some more capable hands may be found to fill out the gaps."

Dr. Packard has done well an important service. He has recorded in permanent form a great quantity of historical facts to make the future historian's task easy. He has also produced a work that the present-day reader will find interesting and useful, no matter in which phase of medical history he is interested.

Der Herzalternans. By Dr. Med. Bruno Kisch, Ord. Professor der Physiologie an der Universität Köln. Price, 1.2 marks. Pp. 214, with 54 illustrations. Dresden: Theodore Steinkopff, 1932.

This monograph is, in deed and in truth, an exhaustive presentation of what is known (and of most that is thought) about the subject of alternation of the heart. Written by a physiologist who has contributed extensively to the experimental investigation of alternation, the theoretical and experimental aspects are surveyed with comprehension and are presented briefly and accurately. No phase of the relationship of alternation to the various types of cardiac disease or to abnormalities of rate or rhythm is omitted. The literature has been scrutinized from the time of Traube, who, in 1872, first differentiated the pulsus alternans from the pulsus bigeminus. The historical matter presented is an interesting commentary on the acumen of the clinicians of the latter half of the nineteenth century, and the ingenuity and scientific spirit of the men who have developed the methods of modern physiology. Approximately one third of the book is devoted to the results of the study of alternation by the usual procedures of physical examination and the aid of various modern mechanical methods. Consideration of the mechanics and the nature of alternation is followed by the author's explanation of his coefficient of cardiac alternation. Fundamentally, alternation is an expression of bio-energetic states of the cardiac muscle which may result under various influences. The clinical section is brief, but the application of the earlier discussions to the clinical problems is convincing and illuminating. Indeed, the entire monograph is so interesting and valuable to the clinician that, to the reviewer, a separate section on the clinical aspects of the subject came as somewhat of a surprise. The clinical section embraces a review of the literature by a master of the experimental and purely scientific aspects of the subject. This little book is a valuable addition to the literature of cardiovascular disease; it is scholarly and succinct, yet complete, characterized by its unity of thought and clarity of expression. An extensive bibliography adds to the value of the book.

Quantitative Clinical Chemistry. Volume I. Interpretations. By John P. Peters, M.D., M.A., Professor of Internal Medicine, Yale University, and Donald D. Van Slyke, Ph.D., Sc.D., Member of the Rockefeller Institute for Medical Research. Cloth. Price, $12. Pp. 1,269, with many tables and figures. Baltimore: Williams & Wilkins Company, 1931.

This volume represents the results of an exhaustive study and compilation of the numerous studies on chemical composition of the blood and urine and the interpretation of the values from the general biochemical, physiologic and clinical points of view. It is an excellent treatment of an involved subject that is in a continuous state of flux. In fact, some of the methods on which certain values of

the chemical composition of the blood are based are so nonspecific and frequently so inaccurate that when interpretations are made these limitations should be emphasized. Unfortunately such methods are changed so frequently by various workers that even an empiric comparison of the results from various laboratories cannot be made without some reservations or assumptions. The book obviously is written so that it should be of interest and value to the alert clinician as well as to his academic colleague. In each of the twenty-one chapters the more fundamental biochemistry of the particular subject under discussion is reviewed briefly without being too elementary; then follow in order comments on metabolism, the chemical composition of the blood and urine, and the clinical considerations in pathologic conditions. An extensive bibliography is added at the close of each chapter. The best chapters are devoted to: (1) hemoglobin and oxygen, (2) carbonic acid and acid-base balance, (3) chlorides, (4) total organic acids and total base. Why the curious statement that cholesterol contains choline was made is a mystery. An extensive and excellent index makes the work extremely valuable.

Prohibiting Minds and the Present Social and Economic Crises. By Stewart Paton, M.D., Lecturer on Psychiatry, Johns Hopkins University, Baltimore. Price, $2. Pp. 198. New York: Paul B. Hoeber, Inc., 1932.

Although dedicated to the "Therapeutic Club," this is not a medical book but a philosophical essay by an author eminent in biology and psychiatry. It touches on the field of mental hygiene, in which Paton was one of the pioneers, and it is undoubtedly his passion for sane thinking that has driven him to write this book. He deplores present-day squandering of nervous energy and the fast pace that does not give people time to balance their emotional and mental budgets. The people who advocate prohibitions of all kinds are characterized as "neurotics, as feelers not thinkers, who are as unprepared as children to direct the course of events in the political, economic or social world. Whatever does not meet with their approval they try to prohibit. Driven by fear of the past and bewildered by the present state of affairs they are swept off their feet by waves of prohibiting mania." "The mental reactions of the leaders of Prohibition in America and Communism in Russia constantly remind us of the emotional attitudes of disobedient children, haunted by Father images and obsessed by fear of parental discipline. Lacking in real independence they think that the control of human activities is merely a matter of authority, in which visions of governmental, ecclesiastical or legal representatives take the place of Father images. The fear that the Prohibitionists have of alcohol has been as effective as the Communists' fear of capitalism in preventing a great many people from becoming temperate, sane and peaceful." These quotations from the preface indicate the scope of the book, which is divided into three chapters: (1) Civilization—Shock; (2) Remedies; (3) Educating the Intellectuals.

Problème sous-hepatiques. By Gaston Parturier. Price, 32 francs. Pp. 272. Paris: Gaston Doin, 1931.

The author considers three problems in the subhepatic region: anatomy, pain and tumors. He spends considerable time emphasizing the fact that the relationship of the gallbladder to adjacent structures in the living subject is different from that observed in the cadaver. The relationships also change with different positions of the body and with pathologic processes. He advises the use of the Trendelenburg position for examination.

Acute and chronic painful conditions in the subhepatic region are discussed, and differential diagnosis is considered. Three types of pain in the gallbladder are described. One is mechanical, owing to the passage of gallstones, another is caused by infection, and the third, "colloidoclosique," is due to an unstable vegetative nervous system and endocrine factors. Treatment is given as follows: for the mechanical type, injections of morphine; for the infectious type, opium, antipyrine

for the fever (given by enema if necessary) and local applications of heat, and for the third type, local applications, with the injection of cocaine. Opiates are contraindicated in the last form.

The importance of laboratory work, especially duodenal drainage and radiology, is emphasized in connection with chronic conditions and tumors. It is advised that patients with the latter conditions, with certain exceptions, be treated first by rest, diet and proper medication. If these are not successful, if jaundice persists or if a tumor grows, surgical intervention is indicated.

This book may be summarized as a fair clinical review of conditions in the upper part of the abdomen.

Nutrition. Volume 1. No. 4. Direction of P. Carnot, M. Loeper and M. Villaret. Price, 150 francs per year. Pp. 367 to 466. Paris: Gaston Doin, 1931.

This is a periodical published six times a year, containing papers on clinical, biologic and therapeutic subjects. Volume 1, no. 4, 1931, is devoted to the gallbladder. It contains articles entitled as follows: "The Influence of Certain Pharmacodynamic Agents on the Contractility of the Gallbladder," "Biliary Disinfection," "Medication for Relaxing the Gallbladder," "Medical Treatment of Chronic Cholecystitis Without Stone," "Hepato-Biliary Action of Vichy Water Collected at the Spring and Tested by Duodenal Tubage, and "Hydromineral Treatment of Hepatic Insufficiency."

In discussing biliary disinfection, the statement is made that sodium bicarbonate changes the p_H of the bile and creates a sterility of the biliary passages, and that hence it is of therapeutic value in cases of chronic hepatitis and cholecystitis. The evidence offered is quite inadequate. The author of the section states that Vichy water is a definite chologogue. This conclusion is based on detailed analyses of bile obtained by duodenal drainage, but again the data given are insufficient. Hydromineral therapy is recommended for the treatment of chronic disease of the liver and gallbladder, but satisfactory evidence is not presented.

Several abstracts of the current literature on the gallbladder are included in the publication.

Krankheitsanfänge bei chronischen Leiden. Herausgegeben von Prof. Dr. A. Fraenkel. Price, 4 marks. Pp. 174. Leipzig: Georg Thieme, 1931.

This monograph contains seventeen articles, each by a different author, and all concerned with the earliest manifestations of a group of chronic diseases.

Fraenkel's article opens with a general discussion of the subject. There follow a chapter on health examinations, life insurance examinations and then a brief discussion of the earlier manifestations of chronic nephritis, thyrotoxicosis, diabetes mellitus, cardiac decompensation, digitalis in early heart failure, the dynamics of cardiac failure, predominating manifestations of schizophrenia, psychosis, the beginning of alcoholism, early manifestation of tabes and paresis, early pulmonary tuberculosis, hepatic insufficiency and fundamental liver diagnosis.

The various subjects have been gone into thoroughly, and the reader may find in this monograph a good critical review of the present knowledge. This volume supplies an actual need, and furnishes a much needed ready reference on this field. Apparently all the contributors are well informed on their special topics and carried on more or less intensive research.

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